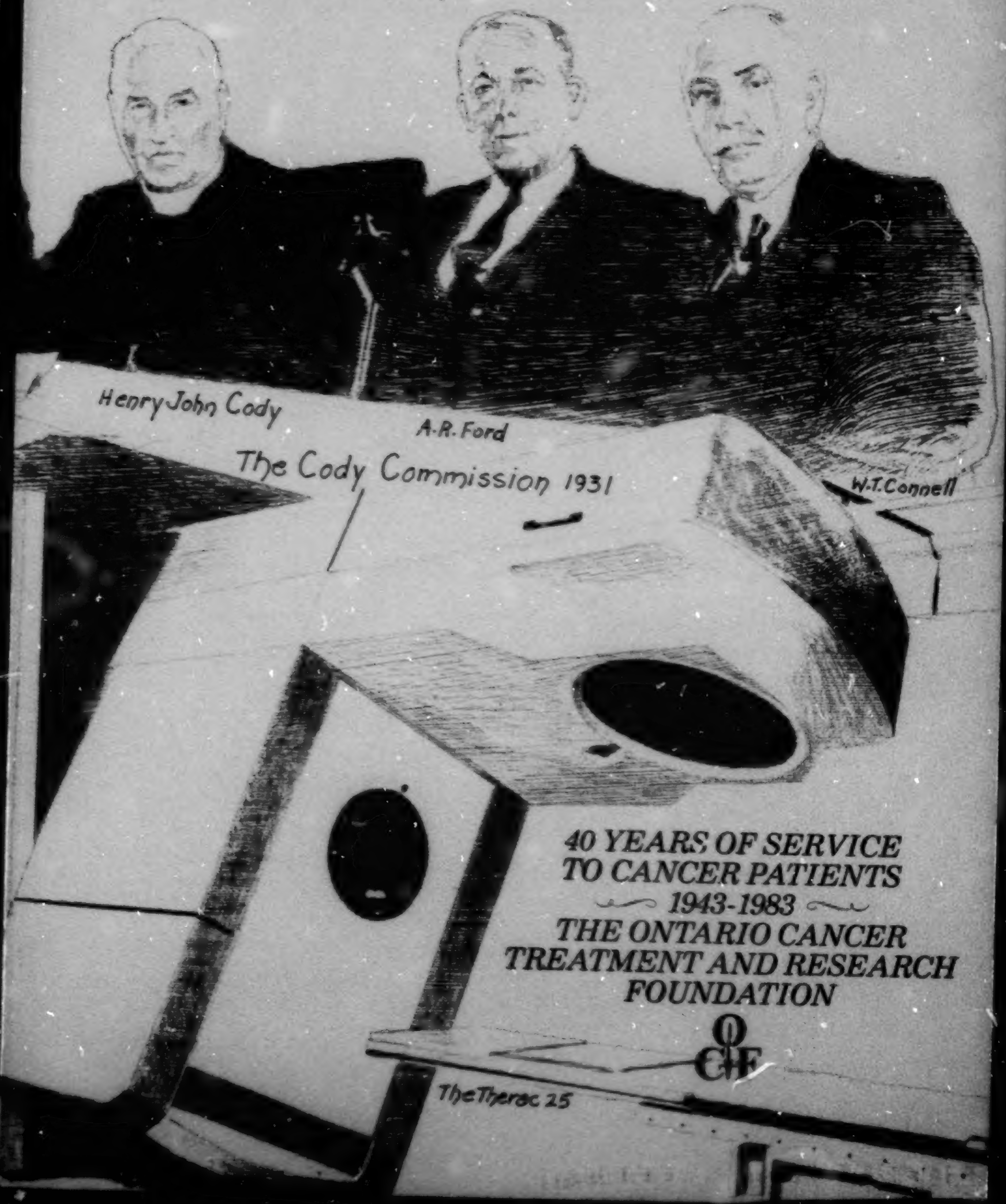
CANCER IN ONTARIO
1983


Henry John Cody
A.R. Ford
The Cody Commission 1931
W.T. Connell
The Therac 25

**40 YEARS OF SERVICE
TO CANCER PATIENTS
1943-1983
THE ONTARIO CANCER
TREATMENT AND RESEARCH
FOUNDATION**

84-4139/

The Ontario Cancer Treatment and Research Foundation was incorporated in 1943 by an Act of the Legislature of the Province of Ontario and reconstituted by The Cancer Act, 1957. The Cancer Act states that, "The object of the Foundation is to establish and conduct a program of research, diagnosis and treatment in cancer, including,

(a) the establishment, maintenance and operation of research, diagnostic and treatment centres in general hospitals or elsewhere;

(b) the transportation of patient and escorts to its treatment centres or to the hospital of the Institute for diagnosis, treatment or investigation;

(c) the establishment, maintenance and operation of hostels in connection with its treatment centres or the hospital of the Institute;

(d) the laboratory and clinical investigation of cancer problems;

(e) the co-ordination of facilities for treatment;

(f) the adequate reporting of cases and the recording and compilation of data;

(g) the education of the public in the importance of early recognition and treatment;

(h) the providing of facilities for undergraduate and postgraduate study;

(i) the training of technical personnel; and

(j) the providing and awarding of research fellowships."

Part II of The Cancer Act, dealing with The Ontario Cancer Institute, as amended by The Cancer Amendment Act, 1968-69, provides that the Institute Board shall consist of 15 persons appointed by the Lieutenant Governor in Council. Five members of the Institute Board shall be representatives of the Foundation, one of whom shall be the chairman of the Foundation. The Act specifies that one of the Foundation representatives on the Board of the Institute shall be the chairman of the Institute.

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CANCER IN ONTARIO

1983

THE COVER

We count our birthdays from 1943 — the year in which an Order in Council brought the OCF into being. However the "cradle" of cancer control in Ontario was a bare committee room at the Parliament Buildings in Toronto where, in 1931, the present system was born in the minds of Rev. Henry John Cody and his five committeemen. When back and front covers are viewed together, we see in the background, behind the Cody Commission, the newest of the regional treatment centres — the Toronto-Bayview Clinic. In the foreground, from left to right, are shown three symbols of modern cancer control: an early x-ray therapy machine; the "cobalt bomb" — the mainstay of radiation therapy in recent times; and the Therac 25 — so called because it can produce 25 million electron volts of energy.

The Ontario Cancer Treatment and Research Foundation
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MESSAGE FROM THE CHAIRMAN

The year, 1983, marked the 40th anniversary of the establishment of the Foundation and, as its fifth Chairman, I take great pride in the many accomplishments of my predecessors.

In 1984, because the practice of oncology is changing rapidly, the Foundation, in co-operation with the Ontario Cancer Institute, will undertake a study of its role in the delivery of services to cancer patients throughout Ontario. Through this process we will receive guidance, concerning our future directions, from experts in management, the health industry, and from the community at large.

The wise advice of colleagues on the Board is essential to decision making. I wish to thank for their counsel the following members, who have retired: Dr. G. L. Blanchet, Mr. J. M. W. Hunter, Mrs. D. M. McGeachy, Mr. R. J. Prettie, and Miss L. Sabourin. Also I take great pleasure in welcoming to the Board five new members: Mr. G. M. Adams, Mr. G. P. Eligh, Mr. D. H. Hill, Q.C., Dr. C. A. D. G. Hurteau, and Dr. G. R. Walker. I look forward to their participation in all our activities.

Our goals in the control of cancer could not be achieved without the continuing financial assistance of the Government of Ontario, the Ontario Division of the Canadian Cancer Society and the many individuals who help us through their donations and bequests. I thank you all and invite your continuing support in the service of the cancer patient, so as to make 1984 an even more successful year than 1983.

Michael Meighen, Q.C.,
Chairman

THE EXECUTIVE DIRECTOR REPORTS

1983 has been a year of satisfaction and self-examination. Satisfaction derives from reflection on the Foundation's 40 years of service to cancer patients in this Province. During this 40th anniversary year we looked back with pride at some major accomplishments such as the regionalization of cancer treatment especially of radiotherapy, and note that this approach is being emulated by other segments of the health industry. Our Thunder Bay Clinic celebrated its 35th anniversary of service to the people of northwestern Ontario. With the financial support of the Ontario Division of the Canadian Cancer Society the Thameswood Lodge in London was expanded, and a commitment made to a new lodge in Hamilton. Also 1983 was a time to take satisfaction in the Foundation's contributions to research and development, notably the clinical application of cobalt-60 energy to radiotherapy, the vinca alkaloids to chemotherapy, lessons from cell biology to bone-marrow transplantation, the development of an artificial larynx (voice box), and orderly classification of human neoplasms. After more than a decade of effort, 1983 saw the creation of a functional and timely Ontario Cancer Registry, which will provide information on cancer incidence, prevalence and mortality by region; such a resource is essential for research into the cause and prevention of cancer, and for the orderly planning of services to cancer patients. Also, the Registry will provide survival information by which to monitor quantitatively the quality of treatment over time; thus if we are not able to improve patient survival, we will know that we are not and will be able to ask "why"? The year also saw introduction in our clinics of computerized patient management system, which is designed to improve efficiency, and to provide a basis for the assesement of the quantity and quality of patient care.

Self-examination is essential if we are to guard against complacency. In 1972, a role study of the Foundation provided guidance for the 1970s. Over the decade which has passed, progress in cancer research, diagnosis and treatment has made it possible for us to do more for patients and in the process has raised public expectations. The decade also demonstrated that fiscal resources are becoming limited. Consequently, in 1984, in co-operation with the Ontario Cancer Institute, we are undertaking a province-wide study of our individual roles in the delivery of high-quality cancer services to a degree of sophistication and at a cost which the public could be expected to support.

During the year, a review of the Foundation by the Standing Committee on Procedural Affairs of the Legislative Assembly of Ontario gave further stimulus to this process of self-examination. The Committee has recommended that:

- The Ontario Cancer Treatment and Research Foundation give the development and completion of the Cancer Registry project its highest priority.
- The proposed role study of the Foundation and its activities be undertaken and

that the relationships between the Foundation and the Canadian Cancer Society and the hospitals, particularly teaching hospitals, be included as part of the study.

- The Foundation seek to establish a cancer clinic in north-eastern Ontario at the earliest opportunity.
- The *Cancer Act* be amended to give the Foundation a broad mandate to educate the public with respect to causes of cancer, its prevention and treatment.
- The Ontario Cancer Treatment and Research Foundation co-ordinate a continuing educational campaign directed at children at the elementary school level with respect to the health hazards of smoking.

These recommendations are now under review.

In 1983 the most notable advance in the delivery of regionalized treatment was the unveiling, by the Minister of Health, of the first commercial 25 MeV linear accelerator at the Toronto-Bayview Clinic. This accelerator of unique design was manufactured by Atomic Energy of Canada Ltd. Similar machines will be installed in Hamilton and London in 1984.

Planning continues with the Ontario Cancer Institute and the Laurentian Hospital to develop a regional cancer program in Sudbury.

The year saw the phasing out of our grants program and the development of our career scientists program with the appointment of three scientists in the London Clinic and one in the Ottawa Clinic, funded in part by the Terry Fox (Ontario) Fund, a generous gift from the Government of Ontario. Our Ontario Clinical Oncology Group (OCOG) centered at the Hamilton Clinic and at McMaster University was further developed and is beginning its first clinical trial in breast cancer. The OCOG is supported by an allocation by the Government of Ontario from Provincial Lottery funds. Our research program is detailed in this volume in the section entitled "Research Programs".

Education programs continue and will be dealt with in the "Education" section.

In Appendix B of this volume are recorded the scholarly publications of staff and grantees.

The brain and heart of any organization are its people. The year saw a number of faithful employees retire and new faces join us. Particularly may I welcome Dr. G. E. Catton as Director of the Ottawa Clinic.

In closing I wish to thank the Chairman, the Members of the Board, and all the staff of the Foundation for their faithful and vigorous support.

JWMeakin

J. William Meakin, M.D., C.M., M.A., F.R.C.P.(C)
Executive Director

No annual financial statement is included in *Cancer in Ontario* but a copy of such statement will be provided upon request to the head office of the Foundation.

PROGRESS IN CANCER

THE MOLECULAR BASIS OF ACQUIRED RESISTANCE OF TUMOR CELLS TO METHOTREXATE

GORDON RICHARDS MEMORIAL LECTURE 1983*

J. R. BERTINO, M.D.**, *New Haven, Connecticut, U.S.A.*

Although the development of additional effective drugs and combinations of these drugs have markedly improved the therapy of acute leukemia, drug resistance remains a major obstacle to cure of patients with this disease. Thus 90% of patients with acute lymphocytic leukemia (ALL) and 70% of patients with actue non-lymphocytic leukemia (ANLL) achieve a complete remission with drug combinations. In contrast, five-year disease free survivals in these diseases are 50% and 15%, respectively. Retreatment with the same agents is less effective, almost certainly because of development of drug resistance. The understanding of the detailed mechanisms whereby cells become resistant to these drugs should allow development of therapeutic programs that obviate this problem, or suggest new therapies directed toward selectively eradicating resistant cells.

Table I lists chemotherapeutic agents in common use for the treatment of acute leukemia and mechanisms by which mammalian cells have been reported to develop resistance to these agents.

In most instances, drug resistance is a result of emergence of pre-existent mutants that survive as a consequence of the selective pressure exerted by these agents. Resistance may develop by diverse mechanisms; some cells selected for high levels of resistance may have more than two causes of resistance, e.g. impaired transport and elevated levels of enzyme, or elevated and altered levels of the target enzyme. In this circumstance, the second presumed mutation has been noted to occur after development of partial resistance by the first mechanism, rather than simultaneously.

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*Presented at the Ninth Clinical Cancer Research Conference, September 27, 1983, held at Geneva Park, Lake Couchiching, Ontario.

**American Cancer Society Professor of Medicine and Pharmacology, School of Medicine, Yale University, New Haven, Connecticut, USA.

TABLE I

Mechanisms of Cellular Resistance to Antileukemic Drugs

Methotrexate	Impaired transport Altered DHFR Elevated DHFR
Prednisone	Altered cytoplasmic receptor
Vincristine	Impaired transport
6-mercaptopurine	Decreased activation to nucleotide
Daunomycin	Impaired transport
Cytosine arabinoside	Decreased deoxycytidine kinase

Cell culture systems and transplanted experimental tumors have been valuable models for studies of drug resistance, since highly resistant lines may be developed, and the mechanism(s) of resistance elucidated. In the clinic, of course, because of the narrow therapeutic index of most drugs employed, relatively small changes (e.g., a 2-4 fold elevation in a target enzyme), may produce "clinical" resistance. In this circumstance, resistance is more difficult to detect biochemically, unless sensitive assays that can measure these small changes are available.

Methotrexate (MTX) is a key drug in the treatment of patients with ALL: in contrast, because of its low activity as a single agent, or in combination regimens, it is not considered to be a useful drug in the treatment of patients with ANLL. Limited uptake of MTX by myelocytic leukemia cells, presumably due to an efficient efflux of the drug, as well as rapid "induction" of DHFR may be important factors in the natural resistance to MTX. We have suggested that the increase in total dihydrofolate reductase (DHFR) that occurs when immature leukocytes are exposed to MTX is a consequence of drug binding and protection of DHFR from proteolytic degradation. A recent study using human KB cells, resistant to MTX came to a different conclusion, namely that the increase in DHFR noted was modulated at the translational level, or by as-yet-undefined post-translational mechanisms.

Another determinant that may play a role in natural or acquired resistance is polyglutamylation of MTX. This process results in accumulation of polyanionic forms of this drug (the addition of up to three additional glutamates in γ-carboxyl linkage). Thus cells capable of rapidly converting intracellular MTX to polyglutamate forms appear to be more susceptible to this drug.

Three mechanisms by which cells acquire resistance to MTX have been documented experimentally in mammalian tumor cells: (a) an increase in DHFR activity; (b) an altered DHFR with less binding affinity to MTX; and (c) impaired transport of MTX.

Acquired MTX resistance of blast cells from patients with leukemia may be demonstrated by a simple in vitro test in which DNA synthesis (^{3}H-deoxyuridine uptake into DNA) is measured in the absence and presence of MTX. After a one-hour exposure to 10^{-6}M MTX, DNA inhibition of leukemia cells that have not been previously exposed to this drug is greater than 95%. These patients have been studied further, and both an altered DHFR and elevated enzyme levels have been noted to occur in these MTX-resistant leukemia cells. However, since elevated levels of DHFR could occur rapidly as a consequence of exposure to the drug by virtue of "induction", genotypic evidence for drug resistance was difficult to obtain.

One strategy for preventing or eradicating drug-resistant tumor cells that survive treatment with a drug or combination of drugs, is to use another drug or another drug combination with a different mechanism(s) of action. Thus cells surviving the first treatment by virtue of drug resistance might be eradicated by the second treatment. Success of this strategy depends on the relative effectiveness of the second treatment in killing the remainder of the tumor cells, and lack of cross-resistance of the cells to the second treatment.

Another strategy that might even be more specific and effective, is to use drugs that selectively kill resistant cells that emerge as the consequence of the first treatment.

Two general approaches are worth considering to overcome resistance due to decreased uptake of a drug.

MTX is transported in most tumor cells by an active transport system, that functions to transport reduced folates. By modifying the MTX molecule by attaching substituents to the alpha and gamma carboxyls of the glutamate, compounds may be fabricated that are transported by alternate mechanisms. For example, when macromolecules such as albumin and polylysine are coupled to MTX via peptide linkage to the glutamate carboxyls, these compounds are effective in MTX transport-resistant tumor cell lines. Lipophilic derivatives (i.e. the mono and dibutylesters of MTX) that rapidly cross the membrane have also been shown to be effective vs MTX-transport resistant cells.

Potent inhibitors of DHFR have also been synthesized with structures not resembling folic acid, i.e. so called "non-classical" antifolates. These compounds are transported by transport systems that are not folate-carrier mediated. Several of these compounds show promise in experimental testing, and should be in Phase I trials in the clinic soon.

These compounds may be even more effective in MTX-resistant cells than in MTX-sensitive cells. An explanation for this increased sensitivity might derive from the observation that these cells may have less than normal intracellular levels of folate enzymes as a consequence of this transport defect. In addition, the opportunity for selective rescue of normal cells, but not MTX-resistant cells with leucovorin

exists; normal stem cells (bone marrow, GI mucosa) will be rescued by concurrent leucovorin while the MTX-transport resistant cells may not.

Drug resistance remains a major obstacle to the cure of acute leukemia. The understanding of the mechanisms by which cells become resistant to drugs may lead to new therapeutic approaches and offer the possibility of greater selectivity in leukemia treatment.

Complete references are available on application to the author or editor.

CURRENT STATUS OF MAGNETIC RESONANCE IMAGING

R. M. HENKELMAN*, Ph.D., *Toronto, Ontario*

Nuclear magnetic resonance imaging (NMRI) is a new way of making pictures within the human body. NMR pictures can be made of plane sections through the body in any orientation just as if the patient had been sliced open. In contrast to x-ray images, which show most clearly the bony structures, NMR images see only soft tissues. The contrast achieved between different types of tissues is very high, and because tumors tend to show up with a different contrast than their surrounding normal tissue, NMRI may be valuable in the identification of malignant disease. However, a number of different types of magnetic resonance images can be made with differing contrast so that much complex research must be done to establish the best types of magnetic resonance images for various possible diseases. While initially this is confusing, eventually the discriminating application of this richness of information will assist the differential diagnosis in patients who have evident disease but of unknown character. Another advantage of magnetic resonance imaging is that it is done without ionizing radiation and therefore without any hazard to patient, volunteer or physician.

Magnetic resonance imaging is based on a physical principle which is different than any used in medicine before. However in physics, chemistry and biochemistry, nuclear magnetic resonance has been used for many years to obtain detailed information about the structure and environment of molecules. In NMRI, protons within the water molecules in the body behave like small magnets and tend to align themselves with an externally-imposed magnetic field. These aligned magnets can be perturbed from their equilibrium positions and, as a consequence, will generate radiofrequency signals, which can be detected by a coil located around the body. With appropriately applied magnetic field gradients, the operator can determine the spatial location of the protons within the body. By the use of computer-data recording and rather elegant mathematics, he can generate a map of the proton location and display it as a photographic image. Thus, the main features of a magnetic resonance imager are a large cylindrical magnet bore, which produces a static magnetic field, a computer control and data acquisition system, and an image display console. Fig. 1 gives a view of the NMRI system installed at the Ontario Cancer Institute (OCI).

In the Throne Speech, in the spring of 1982, the Ontario government announced its intention to assist the OCI to acquire a prototype magnetic resonance imager. Subsequently, the then Minister of Health, Hon. Larry Grossman provided a grant of

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*Senior Scientist, Ontario Cancer Institute, Toronto.

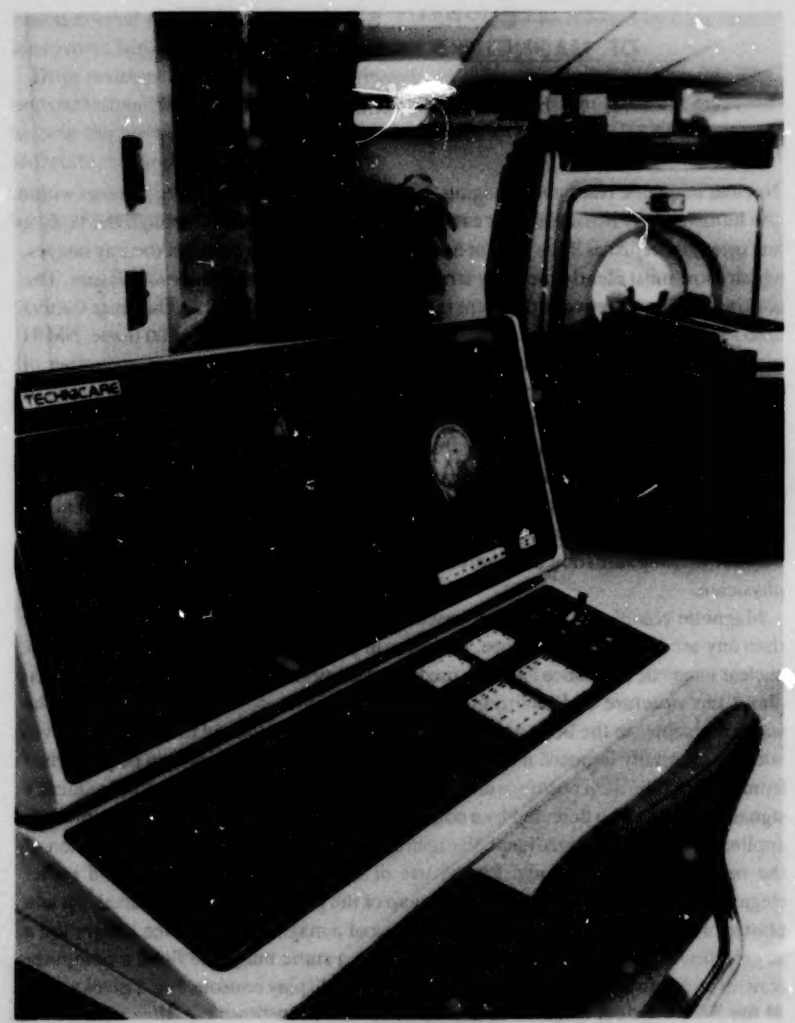

Fig. 1. The magnetic resonance imager at the Ontario Cancer Institute: in the foreground is shown the operator's console and the image screen; in the background the patient table is moving into the bore of the large magnetic field imager. An open and friendly patient environment is possible because there is no need for radiation shielding.

$1.3 million to purchase an imager from Technicare Corporation and have it installed at the OCI. The facility opened on March 1, 1983, and since that time has been used for preliminary clinical investigations. A basic science research program developed in the Department of Medical Biophysics supports clinical research and provides the information necessary to optimize and interpret NMR images of malignant disease. This basic science group is addressing a number of questions related to the science of image formation and image quality in NMR, in an attempt to provide the best possible magnetic resonance imaging for the investigation of cancer patients.

The clinical evaluation program at OCI has focussed on the assessment of the diagnostic accuracy of this new imaging modality. To do this, we are studying several series of patients with known malignant disease with a variety of imaging methods in order to identify the types of images which show up the known disease most clearly. In parallel with this stage, the basic sciences researchers are doing a series of investigations to ensure that the imager is working at its optimal level. After the best imaging methods are established, a series of surgical patients are being imaged and the type and extent of disease as visualized in the magnetic resonance images will be compared with the lesion seen at surgery. The following disease states will be evaluated in this way: 1) the spread of lung cancer into the mediastinum; 2) spread of metastatic disease to the liver; and 3) prostatic carcinoma. These studies will be carried out over the next two years by a team of investigators, which will include diagnostic radiologists, surgeons, radiation oncologists, and scientists from the OCI, Toronto General Hospital, Wellesley Hospital, Mount Sinai Hospital, Toronto Western Hospital and Sunnybrook Hospital.

Already magnetic resonance is providing unique and fascinating images of malignant disease. Fig. 2 is a sagittal image through the head showing a large tumor of the pituitary. Tumors often stand out in distinct contrast from the surrounding tissues, but occasionally are not visualized at all. Each of the large spectrum of available imaging methods yield different results and a great deal of investigation must be done before we can establish clearly the role of magnetic resonance in cancer. However, from preliminary work, it is clear that magnetic resonance will provide a new "window" into the body by which to identify and stage malignant disease. What remains to be demonstrated is the exact role of this new modality in the management of cancer patients.

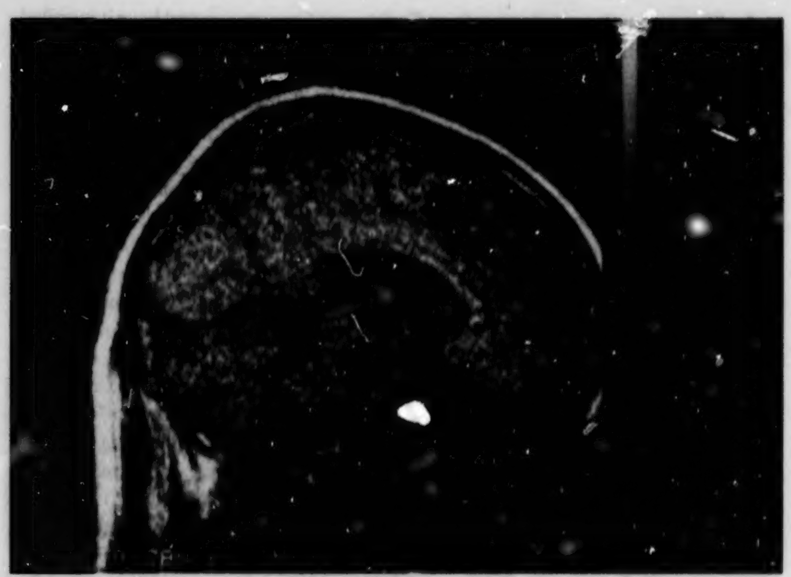

Fig. 2. An NMR image of a vertical plane through a patient's head showing the soft-tissue structure of the brain and ventricles but showing regions of bone as dark. The arrow points out a large pituitary tumor.

BONE-MARROW TRANSPLANTATION: CURRENT STATUS

H. A. MESSNER, M.D., Ph.D.*, *Toronto, Ontario*

Bone-marrow transplants have been performed at the Princess Margaret Hospital since 1970. The original attempts on patients with aplastic anemia and individuals suffering from acute leukemia unresponsive to further chemotherapy indicated clearly that bone-marrow transplantation is most beneficial during early stages of disease. Based on this experience, protocols were designed in 1979 for patients with aplastic anemia, acute leukemia and chronic myeloid leukemia. Currently 48 of 89 patients transplanted since 1979 are alive and free of their primary disease. The main risk factors determining survival include age of the patient at the time of transplantation and status of the underlying disease. The survival of patients transplanted before the age of 30 is significantly better than those older than age 40. This age-dependent probability of survival may reflect altered tolerance to the aggressive preparation of high-dose chemotherapy and total body irradiation. In addition, the frequency and severity of the interaction between donor cells and host organs (graft vs host disease) such as skin, liver, bowel, increases with age. This transplant-related complication may cause mild, moderate or severe symptoms and may lead to the death of the patient. Transplantation during early and stable phases of the disease is more successful than during advanced and therapy-resistant phases.

The observed failures are due mainly to transplant-related complications such as graft vs host disease and fatal, usually viral infections. Recurrence of the primary malignancy was observed only in 4 of 73 transplanted patients with malignant diseases. In all four cases, the transplant was performed during poorly controlled or very advanced stage of the disease.

In summary, bone-marrow transplants can be performed successfully and can lead to long-term, disease-free control of aplastic anemia and hemopoietic malignancies. Improvement of the survival rate requires extensive research to facilitate prophylaxis and treatment of graft vs host disease as well as better control of certain life-threatening infections.

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*Medical Oncologist, Princess Margaret Hospital, Toronto; and Associate Professor of Medicine, University of Toronto.

EDUCATION

SUMMARY OF OCTRF EDUCATION ACTIVITIES

Manpower Shortage of Oncologists in Ontario

Too few oncologists are graduating from Ontario's medical schools to meet current needs and, of the limited number who do choose this specialty, many do not remain in the province. The shortage continues despite the addition by the medical schools of certain "add-back" residency posts, and the Foundation's recent decision to increase its own funding of oncology training posts from two per teaching clinic to three. Of the shortages in the two specialties — radiation oncology (RO) and medical oncology (MO) — the more severe is in RO.

The shortage is exacerbated because an increasing number of trainees in RO, once they have obtained the specialty certification, move to the United States where the level of remuneration is much higher. The Foundation is searching for ways to check this serious loss. Towards this end, the consultants conducting the Joint Provincial Role Study have been asked to "examine the role of the OCTRF and OCI in professional education in the field of oncology and recommend approaches to the organization and funding of such education particularly of professionals in short supply". We expect the consultants' report by September 1984 and eagerly anticipate their recommendations on this important matter.

An urgent practical matter, which will become more acute as we expand oncology training programs in the clinics, is the "freeing-up" of clinical staff time necessary for undergraduate and graduate teaching. In some clinics, understaffing due to unfilled oncology residency posts has imposed heavy clinical workloads and has limited the time available for education and research. As an interim measure, the Foundation has added, to the clinic staffs, non-specialists who function as clinical assistants, providing general care and thus relieving staff oncologists of some of their clinical workload. This, however, is not the optimal solution; the only long-term solution to the shortage of oncologists will be to maximize in the clinics the numbers of oncologists-in-training who, as an integral part of their training, will participate in patient care.

Undergraduate Medical Education

There is an urgent need to expose undergraduate medical students to the clinical practice of oncology through clinical clerkships, electives or studentships. Not only would this exposure stimulate the interest of undergraduates in the specialty of oncology but this experience would introduce the student to the multidisciplinary management of cancer as practised in the clinics and the Ontario Cancer Institute. Since 1963, in the absence of ongoing rotation of the medical students through the clinics, the Foundation, in association with the Ontario Division of the Canadian

Cancer Society, has supported the Ivan H. Smith Memorial Studentships which have met these needs in part at least. The 1983 Ivan Smith Program is described below with an abbreviated report concerning a retrospective study of these awards.

Ivan H. Smith Memorial Studentships

In 1983, in co-operation with the Ontario Division of the Canadian Cancer Society, the Foundation awarded 16 medical undergraduate studentships for periods of 4 to 12 weeks. The programs were undertaken in the regional treatment centres at Hamilton, Kingston, London and Windsor, and in the Princess Margaret Hospital. Fifteen were undertaken outside of the academic year and one — an elective studentship — was taken within the academic year. These studentships introduce the future physicians of Ontario to the many rewarding aspects of a career in oncology. The students are given an opportunity to observe and participate in the regional treatment centres' clinical and research activities and they receive on-site exposure to the multidisciplinary management of cancer patients.

A retrospective study of the period 1963-1982 revealed that 96% of those responding found the program to be a valuable experience, regardless of the physician's subsequent choice of specialty. Also, most of the respondents asserted that, outside of their studentship experience, the quality and quantity of the exposure to oncology provided in the undergraduate program was insufficient, both in quality and quantity. After its final analysis, the results of the study will be communicated to the medical schools for their information. Our Sub-Committee on Undergraduate Medical Education will continue its close study of undergraduate medical education in Ontario's universities as it relates to oncology.

The Harold E. Johns Fellowships in Medical Physics

In 1983, for the third consecutive year, the Foundation was able to offer summer studentships in medical physics. This program, supported by a special cancer services improvement grant from the Ontario Division, Canadian Cancer Society, aims to increase the numbers of medical physicists in Ontario, so as to meet the high technology needs associated with diagnosis, treatment and research in cancer.

The 11 studentships awarded in 1983 were taken at the following regional treatment centres: Hamilton, Kingston, London, Ottawa, Thunder Bay, Toronto-Bayview, Windsor, and the Ontario Cancer Institute incorporating the Princess Margaret Hospital.

Since 1982, due to fiscal constraints, the Foundation has not been able to fund a competition for the postdoctoral and graduate fellowships in medical physics. One postdoctoral and two graduate fellowships were awarded in 1982. It is a pleasure to report that one of the graduate fellows, Michael Patterson, who recently completed his Ph.D., has accepted the position of medical physicist at the Hamilton regional centre. Michael Wood, the other graduate student, continues in his program in the

Department of Medical Biophysics at U of T. The postdoctoral fellow, Dr. W. P. Jeeves, is conducting research at the Hamilton regional centre and will complete his fellowship in June 1984. We gratefully acknowledge the support of Ontario Division, Canadian Cancer Society of this program.

Continuing Professional Medical Education

Currently the Foundation is looking into ways and means of enhancing its contribution to continuing professional education in two constituencies — family physicians and specialists — especially those practising outside the teaching centres. This matter is made urgent by rapid advances in the management of cancer. The Foundation is considering a number of undertakings, including publication in a national journal of an "oncology update". In addition, the Foundation, in co-operation with the Ontario Division, Canadian Cancer Society and the Ontario Ministry of Health, is exploring the feasibility of a Directory of Cancer Services. This directory, which will list the many aids, techniques, services and benefits available to the cancer patient, will be circulated widely in the community, especially to physicians, other health professionals, referral agencies, and libraries. The project is being supervised by Dr. John O. Godden, Editor of Publications, who believes that this directory will make the system more comprehensible and consequently will assist all concerned to make more effective use of such services. Initially, Dorothy Davey, R.N., is working under contract to produce a prototype to cover Metropolitan Toronto; however, the goal is to produce a directory that will describe cancer services throughout the province.

Also, the Foundation is discussing with the Ontario Division, Canadian Cancer Society, a joint pilot project for the provision of a "phone-in" cancer information service. This service, proposed by Dr. W. Hryniuk, would be housed in the Hamilton regional centre and would disseminate information about cancer on an open-line basis. The service would have a computer base and could be reached by telephone from anywhere in Ontario and would serve both public and physicians.

In addition to the foregoing, the Foundation is pleased to report that the clinics and the Princess Margaret Hospital have carried out an active program of continuing education throughout 1983. Clinical days and seminars were organized, guest lectures hosted, and numerous lectures were given in each community by members of the clinic staffs.

On September 27, 1983, the Gordon Richards Memorial Lecture was delivered at the biennial clinical cancer research conference at Lake Couchiching. The lecturer, Dr. J. R. Bertino of the Department of Biochemical Pharmacology at Yale University, New Haven, Connecticut, spoke on "The Molecular Basis of Acquired Resistance of Tumor Cells to Methotrexate". On September 22, 1983, the W. G. Cosbie Lecture was delivered at the Canadian Oncology Society meeting in Calgary; the lecturer, Dr. Oliver Beahrs of the Department of Surgery, Mayo Clinic, Rochester, Minnesota, spoke on the subject "The Surgery of Cancer of the Thyroid".

Two Ontario Cancer Foundation Lectures were given in 1983. On May 19, 1983, Dr. Leslie DeGroot, Head of Endocrinology, University of Chicago, spoke at the Canadian Association of Radiologists' meeting in Quebec City; his subject was "Thyroid Cancer: An Overview". On October 24, 1983, Dr. Sheldon Sommers, a pathologist associated with the Council for Tobacco Research, New York, spoke at the annual meeting of the Ontario Association of Pathologists held at the Chateau Montebello in Quebec. His subject was "Malignancy — Unusual Features". During the year, the Foundation's Head Office held three seminars in epidemiology. These sessions, which are attended by epidemiologists from across the province and by members of the Foundation staff, continue to provide a valuable exchange of information and views. Lastly, in 1983 Foundation grants to Ontario's medical schools supported a number of postgraduate programs with a significant cancer content.

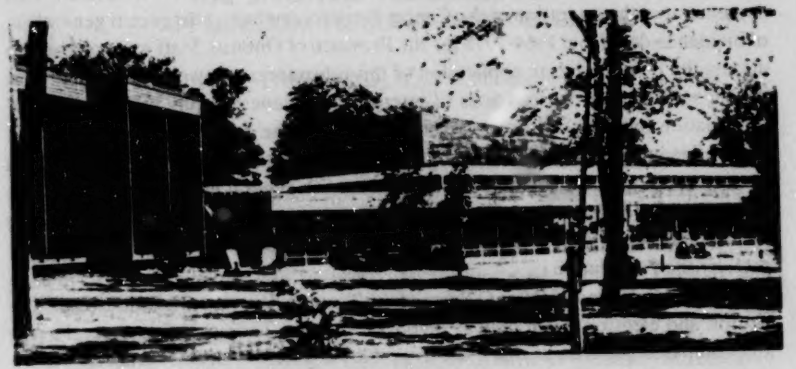
Public Education in Cancer

On September 14, 1983, the Foundation was reviewed by a Standing Committee on Procedural Affairs of the Legislative Assembly, which, at regular intervals, conducts a systematic survey of government agencies. The committee's report contains two recommendations which pertain to education: namely, that the Foundation's mandate under The Cancer Act be expanded to encompass not only the education of the public concerning the importance of the early recognition and treatment of cancer, but also with respect to its causes and prevention. Secondly, the committee recommended that the Foundation, in conjunction with the Canadian Cancer Society, the Ministry of Health, and the Ministry of Education, co-ordinate a continuing educational campaign directed at children at the elementary school level with respect to the health hazards of smoking. Since, from the time of its inception, the Ontario Division of the Canadian Cancer Society has assumed responsibility for public education in cancer, these recommendations are being considered jointly by the Society and the Foundation.

On September 13 and 14, 1983, the Foundation's representatives attended a conference "The Education of People with Cancer" at the Downtown Holiday Inn, Toronto. The conference was hosted by the National Office of the Canadian Cancer Society through its Service to Patients Committee "to lead to a better understanding of the co-operative roles which may be played by the Society and Foundations in maximizing the quality of education services provided to people living with cancer". This conference drew registrants from across Canada.

Mary Lou Erochko

NINTH CLINICAL CANCER RESEARCH CONFERENCE*



Geneva Park — Site of the
Ninth Clinical Cancer Research Conference

The Ninth Clinical Cancer Research Conference was held from September 26 to28, 1983 at Geneva Park, Lake Couchiching, at a time of ideal Indian summer.

Although attendance was down slightly from the 1981 conference, 180 guests attended and several others, who were unable to attend for the entire meeting, came for special sessions on Tuesday or Wednesday. Most of the guests arrived on Monday evening and the program was arranged by Drs. G. P. Browman and W. M. Hryniuk of the Hamilton Clinic. The theme of the conference was "Strategies to Overcome Tumor Resistance". In keeping with this theme, Dr. R. M. Sutherland, University of Rochester Cancer Center, opened the sessions on Tuesday morning speaking on "Experimental Models in Cancer: The Spheroid Tumor Model — Application to Clinical Problems". This was followed by two simultaneous scientific sessions (two topics per session) which addressed: i) Strategies to Overcome Radiation Resistance; ii) Problems in Drug Delivery; iii) Monoclonal Antibodies in Tumor Detection and Therapy; and iv) Biochemical-Pharmacological Strategies. Dr. J. M. Goldie, Cancer Control Agency of British Columbia, addressed a plenary meeting on the subject "Clinical Testing of Experimental Models: Rationale for the Use of Alternating Drugs as a Strategy to Deal with Drug Resistance".

A record number of 48 posters were on display in the Conference Centre. The respective authors were available from 2:00 to 3:30 p.m. Tuesday to discuss their projects, which covered the wide spectrum of cancer research being conducted throughout the province.

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*Held at Geneva Park, Lake Couchiching, Ontario, September 26-28, 1983.

In addition to the general poster session, four special displays were set up in Geneva Court. Dr. E. A. Clarke and members of the OCTRF Research Unit demonstrated the operation of the Cancer Registry, including the recent generation of incidence data from 1964-1975 for the Province of Ontario. Staff were on hand to discuss the possible future application of this information, as well as incidence and cancer mortality on various sites of interest. Mrs. June Murphy and members of Information Systems demonstrated the features of the newly-installed Honeywell computers in the Foundation Clinics and their interaction with Head Office. These displays were well attended and responded to with general enthusiasm.

Dr. M.A.S. Jewett presented updated information regarding the activities of the Sperm Bank at the Wellesley Hospital, Toronto — an activity which is supported, in part, by the Foundation.

Howard Micheals and Peter O'Brien of the Toronto-Bayview Clinic illustrated the photon and electron beam data available on the new Therac 25 linear accelerator and compared these data with those available on other linear accelerators.

On Tuesday evening, Mr. M. A. Meighen, Chairman of the Board, introduced Dr. J. R. Bertino, Associate Director, Clinical Research, Yale Comprehensive Cancer Center, who presented the Gordon Richards Memorial Lecture*. Dr. Bertino spoke on "The Molecular Basis of Acquired Resistance of Tumor Cells to Methotrexate". Dr. Bertino's lecture was followed by a panel discussion, chaired by Dr. G. P. Browman.

On Wednesday morning two plenary sessions addressed the topics: i) Clinical trials which test basic principles of cancer treatment; and ii) Basic issues facing the OCTRF.

In his closing remarks, Dr. J. W. Meakin expressed his gratitude to Drs. Browman and Hryniuk for arranging an interesting program, to the guest speakers and to all those who had participated in the various sessions and activities of the conference.

Dates for the 1985 Conference are September 30, October 1 and 2.

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*Abstract of this lecture is included in the "Progress in Cancer" section.

EXPERIMENTAL MODELS IN CANCER: THE SPHEROID TUMOR MODEL – APPLICATION TO CLINICAL PROBLEMS*

R. M. SUTHERLAND, Ph.D.**, *Rochester, N.Y.*

Multicell spheroids are three-dimensional structures of cancer cells, which can be grown in culture to simulate the growth and microenvironmental conditions of intervascular microregions of tumor or of micrometastases. Spheroids have been used to study a variety of problems in cancer biology such as: Factors affecting growth kinetics, cellular interactions, development of necrosis, cellular and microenvironmental heterogeneity, nature and mechanisms of resistance to therapy, and new methods of cancer therapy.

Cellular heterogeneity develops in spheroids due to intrinsic (genetic), and extrinsic (microenvironmental) influences. Direct evidence exists that abnormal vascularization results in a heterogeneous oxygen supply in microregions of human tumors. Such data also indicate that availability of other important nutrients and growth factors would be limited. Spheroids were used to measure the effects of factors in the microenvironment (the culture medium) on the heterogeneity of cellular phenotype and microenvironments. The O_2 concentration gradients, as measured with microelectrodes, were highly dependent not only on the O_2 level in the medium, but also on the supply of other nutrients such as glucose. The pO_2 in the centre of the spheroids decreased as the glucose concentration decreased due to an increased O_2 consumption by the cells to satisfy energy requirements. Central pO_2 values often were significantly above the levels required to induce radiation-resistant, hypoxic cells despite the presence of central necrosis. The fraction of non-proliferating quiescent cells, as measured using flow cytometric and autoradiographic techniques, increased in nutrient-deprived conditions. These quiescent cells were isolated using centrifugal elutriation as well as a selective spheroid dissociation method. The clonogenic efficiency of the most centrally located fraction of quiescent cells ranged from 25% to 50%, depending upon the oxygenation and nutrient conditions of the culture medium. The cells located in the spheroid's central regions were resistant to both Adriamycin and radiation. These data indicate the necessity for additional research to determine the role of cellular microenvironments in the development of quiescence and therapy resistance.

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*Abstract of a paper presented at the Ninth Clinical Cancer Research Conference, held on September 26-28, 1983, at Geneva Park, Lake Couchiching, Ontario.

**Director of Experimental Therapeutics, Cancer Center of the University of Rochester Medical Center; and Professor of Radiation Biology and Biophysics, University of Rochester, Rochester, N.Y.

Other experiments demonstrated cell to cell interaction in spheroids, which also may affect biological characteristics and sensitivity to therapy. Cells in small spheroids (5 to 20 cells) are more resistant to ionizing radiation, heat and ultrasound than are the same cell types grown as two-dimensional monolayer cultures. The radiation resistance is greatest for cells, which "communicate" through gap junctions as measured by the resistance to intercellular passage of electric currents from micro-electrodes. This "communication" decreases for some cell types as spheroids grow, even at relatively small sizes (<300 μm diameter). Another observation, which can be partly explained by some form of cellular co-operation, is the marked decrease (factor of 4) in O_2 consumption in spheroids of V79 hamster cells between 200 and 400 μm diameter in association with the development of quiescence but before central necrosis begins.

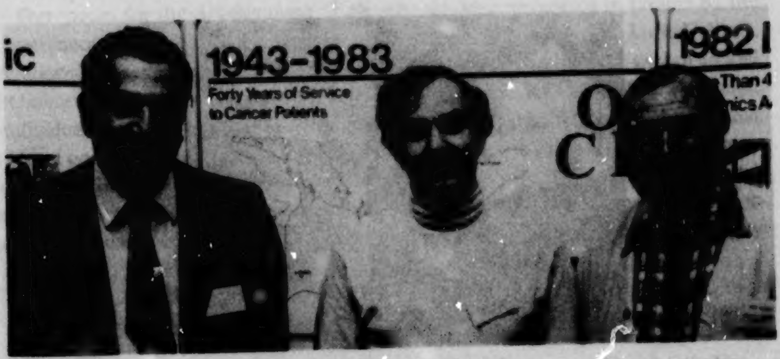
Changes in cellular differentiation were detected in spheroids, which may mimic the clinical situation. Spheroids of human small-cell lung carcinoma change to a large cell morphology after many months in cultures. Associated with these changes is an increased resistance to ionizing radiation, mainly an increase in the shoulder of the survival curve. This observation of increased resistance associated with a change in morphology often has been observed in recurrent tumors of the lung.

It may be possible to exploit altered microenvironments, which are relatively unique for tumors, to activate drugs preferentially. Thus, cells in spheroids, which are resistant to Adriamycin and radiation mainly because of their quiescent state in reductive, low-oxygen microenvironments, can be killed by nitroimidazoles such as misonidazole. Furthermore, these drugs have been shown to interact "supra-additively" with many anticancer drugs, especially alkylating agents. However, in studies in monolayer cultures, nitrosoureas with the greatest relative carbamoylating activity and lowest alkylating activity, such as CCNU, produced the greatest enhancement when combined with misonidazole. Additional experiments are in progress to determine the mechanism of these interactions, and to establish the in vivo effectiveness of such drug combinations.

Thus, in spheroids we can demonstrate modulation of phenotypic expression by cellular microenvironments. The response of the cells to different therapeutic modalities is greatly affected. Further research into the pathophysiology of human tumors will use direct methods whenever possible, but also will use indirect methods such as the multicell spheroid model.

Gordon Richards Lecture Discussants
J. M. Goldie, J. R. Bertino, V. Ling and G. P. Browman

Scientific Session Participants
J. F. Kotalik, R. P. Hill, G. M. Thomas, H. B. Michaels and R. G. Mackenzie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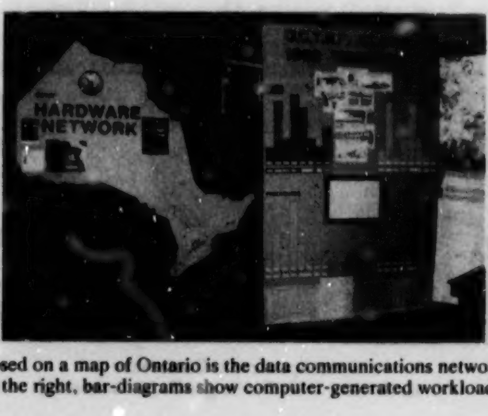
Guest Speakers at Conference
J. R. Bertino, J. M. Goldie and R. M. Sutherland

1943–1983
Forty Years of Service
to Cancer Patients

Ontario Cancer Registry
Loraine D. Marrett, E. Aileen Clarke and Colin L. Soskolne

The colorful jigsaw puzzle shows the many inter-related computerized applications which are at various stages of development.


HARDWARE
NETWORK

Superimposed on a map of Ontario is the data communications network of the OCTRF. On the right, bar-diagrams show computer-generated workload statistics.

RATIONALE FOR THE USE OF ALTERNATING CHEMOTHERAPY AS A STRATEGY TO DEAL WITH DRUG RESISTANCE*

J. H. GOLDIE, M.D.**

A substantial and growing body of evidence suggests that a major factor in preventing chemotherapeutic cure of neoplasms is the development of drug-resistant tumor cells. Such evidence comes from the study of experimental tumors in animals and in vitro systems where one can readily demonstrate specific drug-resistant mutants and from in vitro clonogenic assays of clinical neoplasms[1-4]. In addition, inferences made from the behavior of clinical tumors during therapy appear to argue that the emergence of drug resistance is a major phenomenon in clinical cancer chemotherapy. It is difficult to account for the behavior of tumors, which regress on chemotherapy and then recur while the patient is being maintained on the same treatment, without invoking some type of selection process for drug-resistant variants.

The weight of evidence concerning the origin of drug-resistant variants within tumors suggests that such variants are a consequence of random, heritable changes in the expression of genetic information in the individual cells[5,6], that is, they are spontaneous mutants. Thus their origin is not directly related to the action of a specific drug or drugs on the tumor-cell population but the resistant cells are selected into prominence by therapy, which kills off sensitive cells and leaves behind the resistant subpopulations. Because there is growing evidence that tumor populations may be inherently genetically unstable, they have a substantial capacity to generate over time a large diverse population of phenotypic variants[7]. This heterogeneity with respect to inherent sensitivity to chemotherapeutic agents will make it very difficult to eradicate a large population of cancer cells by drugs.

Our model for the development of phenotypic drug-resistance in tumors by the spontaneous mutation mechanism was based essentially on the classic Luria Delbruk relationships seen in bacterial populations[8]. The broad outlines of such a model indicate the general relationship between tumor mass and curability. Although individual mutational events are random, there will be an increasing likelihood that at least one specific, drug-resistant mutant will arise as the cell population increases with time. In addition, large populations of tumor cells will be more likely to contain at least one resistant phenotype than will smaller tumors. This will be true only on average, because of the random origin of the resistant cells and the small probability that the first mutant will appear early in the expansion of a neoplastic clone and subsequently generate a large number of resistant progeny. Likewise, it also is probable that there may be no resistant cells at the time the clone is subject to therapeutic intervention. In theory the latter case would be curable by the appropriate chemotherapy if this is given with sufficient intensity and for sufficient duration. As has been indicated previously this phenomenon, which is an inherent property of spontaneous mutations, on its own will create a general relationship between tumor burden and curability, and explain the variable response to drug treatment from individual to individual. Of course other sources of variation and othe factors will influence cure over and above those generated by the distribution of resistant phenotypes.

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*Paper presented at the Ninth Clinical Cancer Research Conference, September 27, 1983, held at Geneva Park, Lake Couchiching, Ontario.

**Head, Division of Advanced Therapeutics, Cancer Control Agency of British Columbia, Vancouver, B.C.

An extension of this basic model, which examines the effect of two independent resistant subpopulations arising within a tumor, allows one to evaluate the influence of sequencing chemotherapeutic treatments on likelihood of cure[9]. For example, imagine that, in a tumor-cell population, two classes of resistant cells, each independent of the other: One is sensitive to treatment A but is resistant to treatment B; the other sensitive to B but resistant to A. Thus this minimal model postulates a complete lack of cross resistance between treatment A and treatment B. Further we will assume that either of the resistant subpopulations can undergo further spontaneous change to a double level of resistance, whereby the cells now are refractory to both treatments A and B. The development of such a doubly resistant phenotype would signal a condition of incurability. The object of effective drug strategy should be to eradicate the sensitive cells in the tumor, and each of the singly resistant phenotypes before double resistance and incurability has time to emerge. In this hypothetical situation, treatment A could represent either a single drug or, as is more likely in the clinical situation, a specific combination, which is employed as a treatment unit.

Our problem now is to identify which sequence of A and B will maximize the probability that no doubly resistant cells will emerge before the eradication of the entire tumor population. As a first approximation to a solution to this problem, we can construct a computer program, which will simulate treatment effects by the log-kill mechanism and will calculate, from moment to moment, the probability that any doubly resistant cells will appear. Earlier we have published such a treatment simulation and on an intuitive basis it is apparent that certain strategies will be significantly superior to others[9].

If we use one treatment arm exclusively, we can anticipate that, after an initial, temporary, drug-induced remission, the tumor, by now consisting entirely of cells resistant to the second modality, will start to grow in the face of continued treatment. If one changes to the second modality late in the therapeutic program, one may still eradicate the tumor but there will be a high probability that at least one doubly resistant cell will have emerged during this long elapsed time. Therefore the total probability of cure of the tumor, while not zero, may be very small.

One can readily demonstrate that the most effective way to sequence the two treatment arms, on average, would be to employ them alternatively. This assumes that because of overlapping toxicity etc., we cannot give both treatments simultaneously, which otherwise would be the most effective strategy. Alternating chemotherapy results in the tandem reduction of each of the resistant phenotypes. The overall sensitive population of tumor cells also will be reduced at each treatment cycle. Such therapeutic approaches can be and have been developed intuitively, based on an empiric model of different subsets of sensitive and resistant cells. However, using mathematical approaches it is possible to develop theories about the structure of such therapeutic programs, which might not be obvious from purely intuitive understandings.

If instead of using a computer simulation to evaluate alternating chemotherapy, one applies advanced probability theory, we can show that, given the basic assumptions of the model, the best fixed strategy would be alternating chemotherapy[10]. This will be true for all circumstances and not just for the instances, which were developed as examples. The emphasis here is on fixed strategy because occasionally situations will arise where alternating chemotherapy would not be the best. This exception has to do with the fluctuating sizes of the individual resistant compartments — a variation predicted by the mutation theory. To take advantage of such variation in size, i.e. where on resistant subpopulation is substantially larger than the other, we require specific information about the composition of the tumor. In the absence of such specific data, one must fall back on what strategy is most likely to work on average, namely, the use of alternating chemotherapy.

Further study of the relationships involved in developing the strategy of alternating chemotherapy indicate that, if the approach is to be effective there must be near-quantitative equivalence of each treatment arm, rather than complete lack of cross resistance. This point is important because some of the clinical trials of alternating chemotherapy have tended to assume that the most important criterion was lack of cross resistance and paid less attention to the quantitative equivalence of the second arm. The following examples illustrate the lesser importance of cross resistance. If we assume a third treatment, C, which can be given with either A or B, and which is not cross resistant with either one, and which generates its own specific log kill, we can construct a third program consisting of A+C, B+C, A+C, etc. This regimen would be superior to alternating A B A B because of the additional effect of treatment C. However, in this treatment each arm will now have a degree of cross resistance because C is a common component to each alternating arm. This cross resistance will be enhanced further when a second additional treatment is added, i.e. D, so now one has A+C+D, B+C+D, etc. The treatments containing C, or C+D will be more effective than A or B on their own yet will incur that measure of increased cross resistance. In extreme case where A is totally cross resistant with B but otherwise quantitatively equivalent, each of the treatment arms is now the same so that alteration will produce the same effect as would the use of the single arm on its own. The extent to which each treatment arm is not cross resistant will increase proportionally the effectiveness when the arms are alternated. However, absolute cross resistance is not an essential requirement.

There is nothing magical in the phenomenon of alternation and, strictly speaking, it is not the alternation per se that produces the enhanced therapeutic effect. Rather, we can consider alternating chemotherapy to be one solution to a more general problem of introducing therapeutic diversity early in a treatment program. Thus the well-known example of alternating MOPP with ABVD can be viewed either as MOPP/ABVD alternation at every month, or as a two-month protocol — MOPPABVD, which is not alternated. However, irrespective of how it is viewed, the therapeutic results will be the same in either case. Our theoretical studies on the mathematical structure of chemotherapy protocols indicate that the important entity, which is enhanced by alternating chemotherapy, is what might be described as "treatment density". A program of MOPP alternating with ABVD differs from straight sequential MOPP because of the additional chemotherapeutic agents, which are introduced in the second month of therapy. If one examines both protocols over a two-month interval, the alternating program employs a greater diversity of therapeutic agents. Studies still underway suggest that measures, which will introduce diversity as early as is feasible and, at the same time, will diminish treatment intervals may also maximize this treatment density effect.

In conclusion, if one assumes that spontaneous drug-resistant variants are a major obstacle to achieving drug-induced cures, certain chemotherapeutic strategies will emerge as being more effective on average than others. One such strategy is alternating chemotherapy — a method which allows one to increase the diversity of several factors in the program. If this can be done while maintaining quantitative therapeutic effect against the sensitive cells within the tumor and without inducing excessive toxicity, theory predicts a greater likelihood of cure. For this to work however, one must satisfy a number of conditions, several of which have been discussed earlier. Also, each component of the alternating chemotherapy must have a considerable degree of effectiveness on its own. The theory does not suggest that the combination of ineffective programs will somehow produce a greatly augmented therapeutic effect. In fact, the magnitude of the benefit obtained from alternation and similar strategies will be related directly to the effectiveness of each of the individual components.

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STRATEGIES TO OVERCOME RADIATION RESISTANCE

Chairmen: Dr. H. B. Michaels
Dr. G. M. Thomas

Participants: Dr. J. F. Kotalik
Dr. R. G. Mackenzie
Dr. R. P. Hill

In keeping with the theme of this year's conference, this session was devoted to strategies to overcome resistance of tumor to radiation. Rather than attempt to address this broad topic in its entirety, the chairmen chose to highlight three independent approaches to the problem. The speakers presented an overview of each topic, and a general discussion followed. The speakers and titles were: Dr. J. Kotalik (Thunder Bay), "Radiotherapy by Multiple Daily Fractions — Expectations and Fulfillment"; Dr. R. Mackenzie (Toronto-Bayview), "Hyperthermia"; and Dr. R. Hill (Ontario Cancer Institute), "Radioprotectors — Current Perspective".

Dr. Kotalik began by discussing the rationale for multiple daily fractions rather than a standard fractionation schedule for external beam radiotherapy. One advantage is that it may be possible to exploit the fact that radioresistant hypoxic cells are believed to have less capacity to repair radiation damage; the tumor has less time to recover from sublethal radiation damage if dose fractions are more closely spaced. A distinction must be made between the use of a smaller than conventional dose per fraction and more fractions, i.e. "superfractionation", and, on the other hand, the use of conventional size fractions delivered over a shorter total time, i.e. "hyperfractionation". There are also dynamic fractionation regimens. In general, treatments with multiple daily fractionation are tolerated well by patients and involve no significant complications, except perhaps some subcutaneous fibrosis or necrosis at very high cumulative radiation doses. Dr. Kotalik described various clinical trials now in progress to evaluate this modality, and also showed how, in a busy radiotherapy department, patients receiving multiple radiation doses per day could be accommodated along with patients receiving ordinary single treatments per day.

Dr. Mackenzie outlined the mechanisms by which hyperthermia produces cellular toxicity and cell death: these mechanisms likely are damage to cellular membranes and to DNA-repair mechanisms. Hypoxic cells and large tumors, which are resistant to radiation, in general, are more responsive to heat treatment (e.g. 41-44°C for 1-3 hrs). Compared to normal tissues, differential heating occurs in tumors largely due to the paucity of blood vessels in malignant tissue and the lack of thermoregulatory mechanisms in those blood vessels which are present, resulting in the tumor's reduced ability to dissipate heat. Dr. Mackenzie gave an overview of the current status of the clinical experience with hyperthermia. There is a general consensus that hyperthermia may be delivered safely to areas that have already received "tolerance" doses of radiation. To date, almost all studies suggest that heat plus radiation can lead to higher complete tumor responses than either modality alone. However many variables must be considered in designing protocols for hyperthermia treatments, e.g. method of heating, desired target temperature, duration and spacing of heat treatments, method of measuring temperatures in tissues, etc. Also there is the important question of how to optimize the timing of heat treatments with other forms of treatment, especially radiation. Dr. Mackenzie urged caution in the interpretation of data from clinical studies to date in view of limited follow-ups after treatment and the many variables which need to be accounted for when assessing results. Nevertheless he believes that the preliminary data were encouraging and that, once the problems of thermal mapping of intratumor temperatures could be overcome, it would be worthwhile to initiate Phase I and II studies in suitable patients with less than "end-stage" disease.

Dr. Hill reviewed the current perspective on radioprotectors and concentrated his attention on the sulphydryl chemical agent WR-2721. He reviewed and presented data showing that, in mice, protection of the bone marrow, as measured by CFU-S, could be achieved and that the degree of protection depended on the dose of WR-2721 administered. The clinical efficacy of this agent, however, depends on a differential protection between the normal and tumor tissues. Data from early studies suggested differential protection between some tumors and skin. A survey of available literature, however, indicates that protection has also been observed in some experimental tumor lines and that not all normal tissues are protected to the same degree. Depending on the normal tissues considered and the tumor models used, the differential protection factor may be so small as to not be considered clinically useful. Dr. Hill reviewed ongoing Phase I trials of WR-2721 in the U.S. and Japan. He cautioned that the clinical study of WR-2721 will require a careful selection of the types of human tumors and their proximity (location) to various normal tissues. The trial design will call for the application of radiation doses in excess of normal tolerance and the safety of such regimens will depend on actually obtaining expected protection of adjacent normal tissues. As new developments occur in this field, which is still highly experimental, we can expect the development of reliable plasma assays for WR-2721 and the continued screening by the NCI of possible new radiation protector compounds.

PROBLEMS IN DRUG DELIVERY

Chairmen: R. M. Sutherland
I. F. Tannock

Participant: L. Levin

The two papers, given at this session, related to different aspects of drug delivery. First Dr. Tannock focussed on drug diffusion from tumor blood vessels to the target cells in solid tumors. Dr. Levin discussed the possibility of using monoclonal antibodies as a vehicle for delivering drugs to specifically targeted cells.

Dr. Tannock pointed out that the sensitivity to anticancer drugs of nutritionally deprived or hypoxic cells in solid tumors may differ from that of their well-nourished neighbours for the following reasons:

i) drug concentration in their vicinity may be low because of limited diffusion from blood vessels and because of drug uptake by intervening cells;
ii) nutritionally deprived cells proliferate slowly and most anticancer drugs are more active against rapidly dividing cells;
iii) the nutritional environment may influence drug uptake or toxicity.

Dr. Tannock has used the methods of radition biology to study the influence of several anticancer drugs on aerobic and hypoxic cells of two murine tumors. Cyclophosphamide, 5-fluorouracil and mitomycin C did not show a selective effect on aerobic or hypoxic cells in vivo, but Adriamycin was selectively toxic to aerobic cells. This selective toxicity of Adriamycin probably resulted from its poor penetration from blood vessels into tumor tissue. Drugs, which have a selective effect on hypoxic or poorly-nourished tumor cells have the potential to improve the therapeutic index when they are used with radiation or Adriamycin. Misonidazole, and the glycolysis inhibitors 5-thio-D-glucose and 2-deoxy-D-glucose show specific toxicity for hypoxic cells in vitro, but at tolerated doses, are not active against hypoxic cells in solid tumors. Development of better drugs for nutritionally deprived tumor cells requires an improved understanding of the relationship between nutrient deprivation and loss of cell viability. This relationship is under investigation using multicellular tumor spheroids as a model.

Dr. Levin concluded that the theoretical basis for the use of conjugates of a tumor antibody and a drug is appealing although many problems remain to be overcome. These problems include:

1. Drug delivery using antibody conjugates depends on the antigenic expression on the tumor cell. We know that human tumor cells probably have weak antigenic expression. Furthermore it is conceivable that antibody conjugates could bring about a preferential survival of antigen-negative cells; additionally, antibody-induced loss of antigen has been documented and cytotoxic drugs per se may alter cell-surface expression of antigens.

2. We need to know more about the mechanism(s) whereby the drug conjugates exert their effects and how they may allow passage of the drug across cell membranes. The interaction of the drug with lysosomal enzymes following entry into the tumor cell, and tight conjugation which may interfere with its disassociation may both influence the effectiveness of treatment.
3. More in vivo work and Phase I studies are required before one can properly assess the true efficacy of this mode of treatment.

MONOCLONAL ANTIBODIES IN TUMOR DETECTION AND THERAPY

Chairmen: P. B. Dent
B. C. Wilson

Participants: S. K. Liao
I. Boxen
C. S. Kwok
D. E. Bergsagel

The purpose of this session was to review the current status of monoclonal antibodies (MA), and in particular of radioactivity labelled MA, in tumor detection and therapy. The underlying principle is that the high specificity of MA for binding to tumor cells will produce a high concentration of radionuclide in tumor masses, and permit nuclear imaging for detection and localization, or produce a radiation dose lethal to tumor cells.

Dr. Liao reviewed the hybridoma technology which, in the last few years, has led us to expect that we may be able to produce substantial quantities of MA with a high specificity for particular tumors, and a low cross-reactivity with other malignant or non-malignant tissues. He compared the advantages of MA system with techniques based upon polyclonal antibodies, and presented some of his own results with MA for human malignant melanoma, demonstrating the high specificity which can be achieved.

Dr. Boxen began his presentation by showing a range of clinical nuclear medicine scans carried out by "conventional" imaging techniques using a variety of radiolabelled agents. He demonstrated clearly the problems in detecting malignant lesions, both primary and metastatic, and the difficulty in distinguishing between malignant and benign disease. An MA scan showing metastatic deposits in the liver demonstrated the potential of nuclear imaging with this new technology. Dr. Boxen then listed and discussed the possible advantages of MA for nuclear imaging — high specificity, constancy of antigen specificity, availability of large quantities of MA, etc., and also identified its limitations and the problems to be overcome if these advantages are to be realized in practice.

Dr. Kwok reviewed the desirable features of MA for radioimmunotherapy, namely: high specificity, uniformity of expression of specificity, and antibody residence time in the tumor. He compared two possible labelling methods for attaching high energy beta-emitting radionuclides to antibodies, namely iodination and metal chelation. The former has been more widely applied but has the defect of in vivo dehalogenation, i.e. detachment of the label from the antibody. Potentially chelation is a much more powerful labelling method, since it reduces the possibility of label detachment, and makes available a wide range of radionuclides with characteristics that can be selected for good imaging and radiotherapy. In developing radioimmunotherapy, an essential step is to quantitate the amount of radioactivity in the target tumor and other organs; Dr. Kwok discussed the use of single photon emission computed tomography (SPECT) for this purpose. In a manner analogous to x-ray CT scanning, this technique uses a rotating gamma camera, thereby providing three-dimensional tomographic images, and at the same time permitting the measurement of regional MA concentration. Finally, Dr. Kwok showed results he had obtained in calculating the radiation dose to tumors, knowing the uptake and distribution of MA, and the physical characteristics of the radionuclide.

In his role as "devil's advocate", Dr. Bergsagel identified some of the major limitations in the clinical application of radiolabelled monoclonal antibodies. In particular, he questioned the basic concept of "tumor-specific antibody", emphasizing that one should regard these antibodies simply as "tumor associated". In general, he doubted whether we would discover any MA highly specific for single tumor types, or even if MA specific for a primary tumor would necessarily have high specificity for metastatic deposits, because of the known heterogeneity of antigenic expression. The capacity of circulating antigens to bind MA outside the tumor sites remains uncertain at this time. For radioimmunotherapy especially, this could be a serious matter because such binding would lead to an increased dose to normal tissues, thereby limiting the amount of labelled antibodies administered, and thus the radiation dose to tumor.

Finally, however, in spite of the many difficulties that must be overcome before MA can be applied in clinical diagnosis and therapy, Dr. Bergsagel emphasized the impressive potential benefits of this technique.

CLINICAL TRIALS WHICH TEST BASIC PRINCIPLES OF CANCER TREATMENT

Chairmen: H. Bush
R. D. T. Jenkin

Participants: S. Sutcliffe
A. R. Harwood
D. J. A. Sutherland

Dr. Sutcliffe, Division of Radiation Oncology at the Princess Margaret Hospital, believes that the use of response criteria for reporting results of cancer chemotherapy provides only limited information concerning effectiveness. Response was a useful end-point of treatment effect only in situations where complete response correlated with prolonged disease-free survival. Currently, this correlation is found only in lymphomas, testicular tumors and other rare tumors, e.g. choriocarcinoma. For most common malignancies, survival is still the most useful index of treatment effect. When response is used as an end-point, one must take great care when interpreting the definition and measurement of response. Where prognostic factors are identified, their utility should be expressed in terms of response, survival, or both. In large part, the frequent disparity between complete response and survival advantages may be due to the heterogeneity of tumors and their metastases.

Dr. Jenkin, Toronto-Bayview Clinic, described a prospective randomized trial of the treatment of childhood non-Hodgkin's lymphoma. A 10-drug program was compared with a 4-drug program. All patients received standardized CNS prophylaxis and all sites of bulk disease were irradiated. The first principle in this trial was that all patients were eligible. Data from small pilot studies should always be confirmed in large randomized studies before making a strategic decision as fundamental as the principle of different treatments for different subsets of NHL. The second principle was to ask only one simple question when evaluating the treatment of a complex spectrum of malignancies. The trial demonstrated that the two regimens were histology specific with regard to lymphoblastic and non-lymphoblastic disease. This advantage appeared to be lost in patients with localized disease, in whom the total body burden of malignant cells was small. A third principle followed in the study was to maximize data collection related to tumor biology. On the one hand, it was not possible to separate undifferentiated lymphomas into those of Burkitt's and non-Burkitt's type; on the other, one could demonstrate the close association of T-NHL with lymphoblastic disease, and B-NHL with nonlymphoblastic disease. A fourth principle was that, for uncommon disease, one can obtain secure results only by multi-institutional collaboration. Finally, in the context of the conference, it was noteworthy that a 10-drug, alternating, non-cross-resistant drug regimen did not demonstrate overall superiority to a 2-drug alternating regimen.

Dr. Harwood, Division of Radiation Oncology at the Princess Margaret Hospital, discussed the difficulties of studying new modalities of treatment in head and neck cancer. Data from retrospective studies of advanced cancer of the head and neck revealed that a life style associated with cigarette smoking and alcohol posed a major obstacle in improving the results of treatment: such a life style is associated with an accelerated death rate from multiple causes and is accompanied by medical diseases, which severely limit the application of neurotoxic radiosensitizers and many chemotherapeutic agents.

Phase I and II studies with misonidazole revealed that less than 20% of eligible patients were suitable for study with this agent. Phase II studies with bleomycin, cis-platinum and methodtrexate showed a high initial response rate but little evidence to suggest improvement in long-term survival (this combination had been abandoned except in cancer of the nasopharynx where a Phase II trial is ongoing). Dr. Harwood discussed the promising initial results with 5-FU infusion, mitomycin C and irradiation of cancers of the larynx/hypopharynx and described the ongoing prospective randomized controlled clinical trial. The primary objective of this study is to reduce the laryngectomy rate in these patients. In summary, Dr. Harwood believes it most unlikely that any currently available chemotherapeutic agent will have a major effect in improving survival in head and neck cancer patients, principally because of the life style followed by this group of patients. At present, chemotherapy in head and neck cancer must be regarded as experimental and not be used except within the confines of a well-designed clinical study.

Dr. Sutherland, Toronto-Bayview Clinic, reviewed breast trials that take into consideration basic principles of cancer treatment. The groups conducting these randomized trials are somewhat discouraged because the initial promise of increased, relapse-free survival rates has not translated into increased survival. However, a number of parameters have a clear prognostic relationship with recurrence and survival, and evidence was presented that axillary-node status, internal-mammary-node scan data, carcinoembryonic antigen level, and estrogen receptor level are such parameters. Certain adjuvant trials have shown promising results, particularly those of agents that act primarily through hormonal mechanisms. Dr. Sutherland reviewed the trials of Dr. Meakin and his collaborators in Toronto and of Dr. Baum and his collaborators in the United Kingdom: At this time there is no consensus concerning the best approach because, in many instances, the results of different trials are conflicting, particularly regarding the possible relationship of estrogen-receptor level and response to endocrine therapy in the adjuvant setting. The reasons for these discrepancies were not obvious. Nevertheless, at the present time, it is clear that overall survival benefit is marginal. Dr. Sutherland believes that population-based studies are necessary for further exploratory analysis of possible prognostic groupings and treatment modalities, and that further clinical trials that would study only fragments of the total population would only provide more conflicting data.

BASIC RESEARCH ISSUES FACING THE OCTRF

Chairmen: Dr. R. S. Bush
Dr. J. W. Meakin

Participants: Dr. H. Bush
Dr. E. A. LeBlanc
Dr. J. E. Till

In opening this session, Dr. Till noted that since the Role Study was done in 1972, the Ontario Cancer Institute has placed a high priority on the development of interface research in order to foster interaction between fundamental and clinical research, citing the leukemia program, and, more recently, the bone-marrow transplant program, as well as programs in radiobiology and diagnostic imaging. Most recently, interface research has been stimulated through the establishment of a postgraduate training program, supported by a five-year grant from the National Cancer Institute of Canada (NCIC) through the Terry Fox funds. The main objective of this program is to attract postdoctoral fellows, particularly post-M.D. fellows. To date, 14 applicants (nine with M.D. degrees, four with Ph.D. and one with a D.D.S.) have been accepted into the program, fulfilling the proposed ratio of two M.D.s to one Ph.D. because of the inadequate participation of M.D.s in interface research. The major problem in maintaining this program is that, compared to Ph.D.s, M.D.s require an additional stipend. In conclusion, Dr. Till emphasized the need for a continuous review of priorities for research personnel, particularly in a time of fiscal constraint. To provide review, the Ontario Cancer Institute recently appointed a Research Advisory Committee, in addition to a small ad hoc committee.

Dr. Haydn Bush expressed his deep concern about the Foundation's philosophy for the support of cancer research, and his doubts about the mechanisms by which priorities were established for research. He noted that because the Foundation supports research in the clinics, in the Ontario Cancer Institute and, to some extent, in the health sciences centres, it is difficult to define clearly the Foundation's research goals. He does not believe that funds made available by phasing-out the grants-in-aid program would be sufficient to establish a meaningful research unit in each of the university-affiliated clinics. Also in some areas the clinical and other resources and interactions with other scientists may not be sufficient or provide the necessary stimulation to maintain a research unit. In addition, Dr. Bush drew attention to the disparate nature of the various Foundation clinics and their attitudes towards research, suggesting that it might be more beneficial to concentrate research in one or two clinics, rather than distributing it equally among all. He called for the establishment of a small research advisory council, which would operate "at arms' length" from administration and be independent of the various groups competing for research dollars. He emphasized that a research training program is essential if one is to ensure high-calibre basic and clinical research.

In responding to Drs. Till and Bush, Dr. J. W. Meakin commented that it was a difficult decision to phase-out the grants-in-aid program. The Foundation's general aim is to create a research unit in each of the university-affiliated clinics, which will consist of up to four career scientists funded by the Foundation, plus at least two other scientists funded by other agencies. It also plans to increase the number of individuals supported in the health sciences centres from 7 to at least 10. This proposal was submitted to the Ministry in 1982.

In view of this change of direction, the Foundation established a Sub-Committee on Support of Research Personnel in 1983 and already has approved the appointment at the London Clinic of two career scientists who will be supported through the Terry Fox Research Fund (Ontario). In addition to providing salary support, this source will give start-up funds for essential equipment, etc. In the fall of 1983 a competition was held for the appointment of at least one, and perhaps two, research scholars to work in the health sciences centres. Support for successful candidate(s) will begin on July 1, 1984.

During the 1983/84 granting year, the Foundation will spend approximately $4,200,000 on research, including $635,000 for grants-in-aid, $3,182,000 for personnel support, $175,000 for the Ontario Clinical Oncology Group and $208,000 for other purposes.

During the 1984/85 year, discontinuation of the grants-in-aid program will provide approximately $500,000 more for personnel support, but the Foundation must move cautiously in determining the number of research personnel to be appointed, taking into consideration the ongoing costs of such support. If the Foundation is to fulfill its aims, the annual Legislative Vote provided by the Ministry must provide an additional $405,000 for the 1984/85 year.

In addition to supporting effective research units in each of the clinics, the Foundation wishes to initiate a modified grants-in-aid program, to address provincial priorities. As outlined in its submission to the Ministry in 1982, this program would cost about $500,000 per annum, thereby necessitating a further increase in Ministry funding.

The Foundation is eager to establish a research unit at the Toronto-Bayview Clinic and, although space has been "roughed in" for this purpose, approximately $800,000 (1983 dollars) must be found to complete this space. Equipment for the laboratory would cost approximately $1,000,000. In consultation with the NCIC, the Ministry of Health, the Canadian Cancer Society and Members of the Toronto-Bayview Clinic, the Foundation has considered sources of funding, especially those required for completion of the available space. Applications for funds for equipment and operating grants should be submitted to other agencies such as the Medical Research Council, the NCIC, etc. The Foundation and the Toronto-Bayview Clinic are continuing their efforts and hope to establish a research unit in the near future.

Dr. A. E. LeBlanc, Director of the Policy Analysis and Research Branch of the

Ministry of Health, reviewed the changing, highly competitive and fluctuating climate for indirect and direct funding of research by the private and public sectors. He outlined the role of the Ministry in supporting research and looked forward to the establishment of the Ontario Health Research and Development Council. Dr. R. S. Bush chaired the interesting discussion which followed.

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REGIONAL TREATMENT CENTRES

REGIONAL TREATMENT CENTRES

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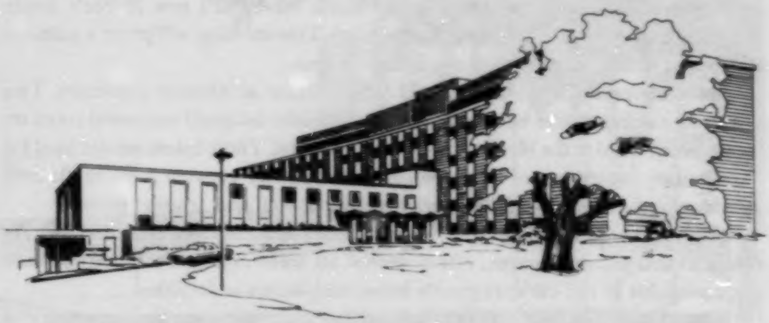
ONTARIO CANCER FOUNDATION HAMILTON CLINIC

HENDERSON GENERAL HOSPITAL



Director:

W. M. Hryniuk, M.D.

Radiation Oncologists:

V. R. Basrur, Ph.D., M.D.
W. Muirhead, M.B., Ch.B.
A. F. Phillips, M.B., Ch.B.
I. Z. Strautmanis, M.D.
A. A. M. Tadros, M.B., B.Ch.

Medical Oncologists:

G. P. Browman, M.D.
A. T. Figueredo, M.D.
M. Levine, M.D.
P. B. McCulloch, M.D.

Physicists:

C. Kwok, Ph.D.
V. G. Peters, B.Sc.
R. H. Price, B.Eng.
B. C. Wilson, Ph.D.

Clinical Assistants:

M. D. E. Goodyear, M.B., B.S.
M. E. McBride, M.D.
C. L. Tanser, M.D.

Administrator:

C. E. Squires

Business Office Supervisor:

C. F. Freeman, R.I.A.

Senior Radiotherapy Technician:

B. J. Walker, R.T.

Nurse Administrator:

H. B. Porter, B.N.Sc.

Head of Medical Records:

D. Armstrong

During the past year, Dr. Michael Goodyear has joined the clinic as a medical oncologist; Mrs. Catherine Squires has taken over new duties as Clinic Administrator; Mr. Clyde Freeman has joined the clinic as Business Office Supervisor; and Ms. Denise Armstrong has been appointed Head of Medical Records.

Plans for construction of a new lodge have been sent out to tender and construction should start shortly. This will add greatly to the comfort of out-of-town patients referred for treatment and also will provide a cost-effective alternative to hospital admission.

Construction has been completed to house the clinic's new 25 MeV linear accelerator from Atomic Energy of Canada Ltd. This machine will prove a valuable addition to radiation facilities in the Hamilton area.

Reconditioning of our 20-year-old 6 MeV linear accelerator continues. Two Selectron machines have been installed in a specially designed treatment room on the oncology ward at the Henderson General Hospital. These machines are used for intracavitary treatment of gynecological cancer and provide a more flexible individualized method, which reduces exposure to staff and hospital patients.

The whole-body CT scanner in the Henderson General Hospital and the computerized gamma camera, with potential for three-dimensional imaging, have made available to our patients greatly improved diagnostic facilities.

The clinic's new area for chemotherapy administration has been opened, and now provides for the patients more pleasant and comfortable conditions. In the chemotherapy area, the Henderson General Hospital provides an on-site pharmacist who, in addition to preparing drugs for injection and dispensing oral medications, assists in patient and professional education.

A third outreach clinic, using the Ontario Cancer Foundation's record-keeping system, will be opened shortly at Cambridge under the direction of Dr. James Gowing.

The 100 KV Picker machine, used for treating skin cancer, has been moved in with the 280 KV Vanguard unit. This change will free two rooms on the main floor for patient examination and minor procedures and will help to relieve an acute space shortage.

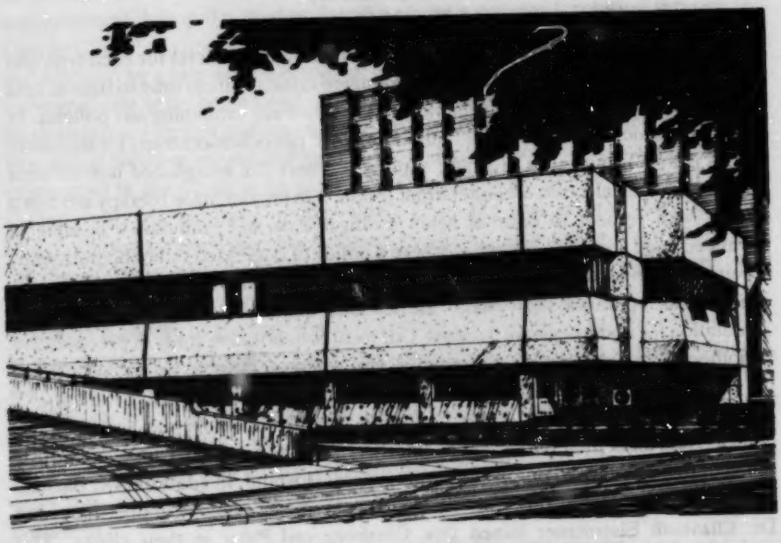
Development continues of a comprehensive psychosocial support program for cancer patients. In collaboration with professionals at the Henderson General Hospital, who are active in pain control and palliative care, we have prepared a booklet "Control of Cancer Pain". The booklet is for the entire spectrum of health professionals engaged in care of cancer patients. For further information, the Department of Nursing at the Henderson General Hospital may be contacted.

In our research, a major emphasis is being placed on improving the treatment of cancer. The Hamilton Clinic now has 464 patients on national trials and 880 on local trials. These studies are described as additional investigations in the Research Programs section of this publication.

W. Muirhead, M.B., Ch.B., D.M.R.T., F.R.C.P. (C)
Senior Radiation Oncologist

ONTARIO CANCER FOUNDATION KINGSTON CLINIC

KINGSTON GENERAL HOSPITAL



Director:

J. S. Lott, M.D.

Radiation Oncologists:

P. J. Froud, M.B., Ch.B.
V. L. Kraus, M.D.
W. M. Ross, M.D.

Medical Oncologists:

B. J. Campling, M.D.
E. A. Eisenhauer, M.D.
P. E. Galbraith, M.D.
A. D. Ginsburg, M.D.
J. L. Pater, M.D.

Career Scientists:

J. C. Kennedy, M.D.
H. F. Pross, M.D.

Clinical Assistants:

M. D. Mulligan, M.B., Ch.B.
D. Pross, M.D.

Physicists:

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P. C. Shragge, Ph.D.

Honorary Medical Consultant:

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Business Manager:

D. Steacy, B.Sc.

Senior Nurse and Radiotherapy Technician:

E. M. Boister, Reg.N., R.T.

Social Service Nurses:

R. Crafts, Reg.N.
C. Keith, Reg.N.

Head of Medical Records:

R. S. Walker

Lodge Supervisor:

N. G. Ambury

In general, the Kingston Clinic has established treatment policies for each type and stage of malignant disease; policies are examined critically from time to time as data on treatment results become available. Currently we are examining our policies: In esophageal cancer — where a program of combined radiochemotherapy for squamous lesions is now in place; in prostatic cancer — where the established non-surgical policies of external-beam and interstitial Iodine-125 implantation therapy are being refined with respect to optimal beam arrangements and cumulative dosage; in advanced head and neck cancer — where a policy of combined radiochemotherapy is being examined in conjunction with the Princess Margaret Hospital; and in breast cancer we are optimistic supporters of the new OCF Clinical Trial of partial mastectomy ± radiation for node-negative patients. Our local collaborative study of preoperative radiotherapy for rectal carcinoma continues, and, wherever possible, we are encouraging the referral of Stage B2 and C rectal cancer patients for postoperative radiation.

In January 1983, Drs. Peter Galbraith, David Ginsburg and Joseph Pater consolidated all of their outpatient chemotherapy in the Kingston Clinic; previously much of this was carried out in Kingston General Hospital. In addition, Dr. Barbara Campling took up a full-time active practice in medical oncology in the Clinic, and Dr. Elizabeth Eisenhauer joined Drs. Ginsburg and Pater in their clinics. This reorganization of chemotherapy services has been accompanied by a significant increase in outpatient chemotherapy in the Kingston region, stressing our needs for more space and staff.

Over the past year, the Kingston Clinic has become increasingly active in clinical research and patient enrolment in NCIC's clinical trials has substantially increased; in order to support this activity, two part-time clinical trials nurses, Debbie Pichora and Ann Voino, have joined our staff. Dr. Pater continues in his role as Director of the NCIC's Clinical Trials Program, in which Dr. Eisenhauer serves as director of Investigational Drug Research. Dr. Froud continues as chairman of the Advisory Council in Radiation Oncology to the Canadian Association of Radiologists. With Drs. John Roder and Susan Cole, Dr. Campling continues an active program of research into developing human monoclonal antibodies to oat-cell carcinoma.

In 1983, the clinic staff strengthened the core program in clinical oncology provided for postgraduate physicians at Queen's University; trainees in all oncologic fields are invited to take all or a part of their training in this program. Presently we have trainees in medical and radiation oncology and in the future we hope that residents in obstetrics/gynecology, urology and surgery will spend a period of their training in this program. Regrettably, the lack of appropriate funding for continuous annual resident recruitment has limited severely the number of residents in both medical and radiation oncology, and this situation seems likely to continue.

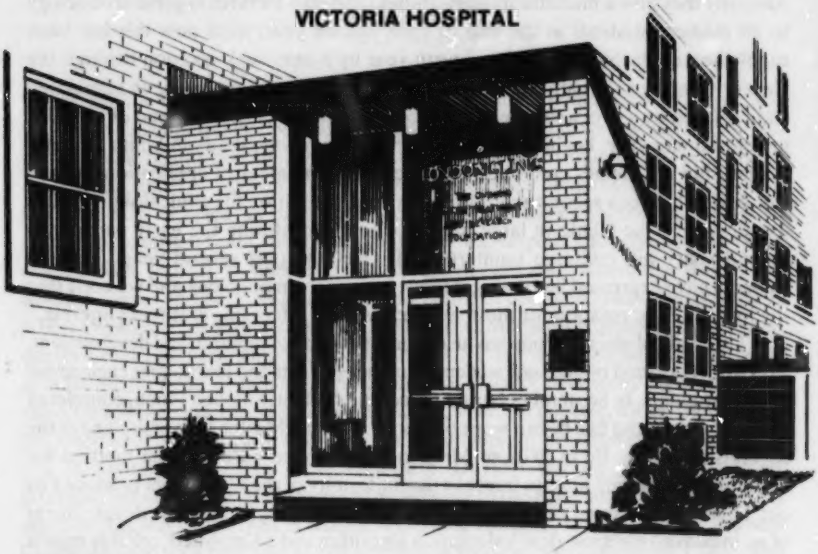
For undergraduate oncologic education, the clinic staff have established at Queen's a more complete program than is available almost anywhere else in Canada. Annually they give a multidisciplinary 16-hour series of lectures in general onoclogy to all medical students at the end of their second year; until now this has been supplemented during the third or fourth year by a one-week rotation through the Cancer Clinic for virtually all students. Recently this rotation has been eliminated and replaced by a two-week elective for one-fifth of the class at the end of the third undergraduate year, beginning in 1984-1985. Fortunately, the Ivan Smith Summer Studentship at Queen's continues to attract a large number of applications for the free period between second and third years; and in addition the clinical skills groups (conducted in the Clinic in large part by Clinic staff during the early part of the second year) will continue uninterrupted. Over the past several years, Queen's students have expressed increasing interest in a career in oncology and we hope that the loss of Clinic rotation for most students will not affect this gratifying interest.

The medical physics group has an ongoing program of research and development. This work is assisted by graduate students, summer students and fourth-year engineering physics students. In September our first graduate student, Stephen Flock, completed his M.Sc. here, and has begun work on his Ph.D. at McMaster University under the supervision of Dr. Brian Wilson. Mr. Flock developed an analytical method for designing a flattening filter to improve the uniformity of the x-ray beam produced by our Therac 20 linear accelerator. Other projects underway include the development of an improved electron-dose calculation algorithm and a simplified, reliable matrix dosimeter.

P. J. Froud, M.B., Ch.B., D.M.R.T., F.F.R., F.R.C.P. (C)
Senior Radiation Oncologist

ONTARIO CANCER FOUNDATION LONDON CLINIC

VICTORIA HOSPITAL



Director:

H. Bush, M.B., B.S., Ph.D.

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P. Banerjee, M.B., B.S.
A. Cheung, M.D.
A. R. Dar, M.B., B.S.
J. A. Gilchrist, M.B., B.S.
J.. A. Hammond, M.D.

Medical Oncologists:

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W. I. Kocha, M.D.
L. Levin, M.B., Ch.B.
R. C. Lohmann, M.D.
J. Skillings, M.D.

Physicists:

D. J. Dawson, Ph.D.
M. Gribble, M.Sc.
J. C. F. MacDonald, Ph.D.

Career Scientists:

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J. Harris, Ph.D.
W. R. Inch, Ph.D.

Terry Fox Fellows:

J. Gardner, Ph.D.
G. Bondy, M.D.

Administrator:

C. Harman, M.H.A.

Business Manager:
E. Micallef

Nursing Co-ordinator:
M. J. Hodsman, B.Sc.N.

Senior Radiotherapy Technologist:
U. Ardy, R.T.T.

Social Worker:
A. Sawarna, M.S.W.

Head of Medical Records:
D. V. Wickett

Lodge Supervisor:
J. Stewart, Reg.N.

The London Clinic has enjoyed an important year of expansion in relation to its staffing, clinical research and basic research programs. The beginnings of a section of neuro-oncology have been now strengthened with the addition of Dr. David Macdonald from the University of Western Ontario, Department of Clinical Neurological Sciences and a clinical research fellow in neuro-oncology. With the generous support of the NCIC through the Terry Fox Fund and the continued support of the Ontario Cancer Foundation, four new laboratories have been added to our research space in the clinic. This expansion in our scientific program has been accompanied by the appointment of three new research scientists, Drs. Ann Chambers, John Harris and James Koropatnik, whose major focus will be in the areas of tumor progression and metastasis.

This year we said good-bye to Dr. T. A. "Sandy" Watson who retired in March 1983. Sandy was Director of the London Clinic for 17 years and has more than earned a well-deserved retirement. We take this opportunity to thank Sandy for all his contributions as director and consultant to the London Clinic over many years. Also in 1983, Dr. David White became Chief of Medical Oncology at the Nova Scotia Tumor Clinic in Halifax. We wish them both well. The acquisition of new staff with an ever-increasing workload has put the London Clinic in the unenviable position of being the smallest cancer clinic in Canada in relation to patient numbers. With the building of phase I of Victoria Hospital now in progress, we look forward to the Ministry's acceptance of our plans so that we can rebuild the London Clinic on the Westminster campus with all expedition. Despite the space shortages we have continued to renovate internally to provide the facilities required in a modern cancer centre.

Our Terry Fox training programs with Dr. Denhardt's cancer research laboratory at the University of Western Ontario continues to flourish with the acquisition of excellent Fellows. We have been fortunate to attract to the London Clinic Drs. Dar and Hammond as consultants in radiation oncology; their presence will do much to relieve our presently overburdened radiation oncology staff.

The rebuilding of the basic research group has permitted us to develop a Clinical Trials Unit and undertake a number of patient studies for the first time. The Unit, co-ordinated by Dr. Cairncross, has begun a retrospective review of all patients with primary malignancy of the central nervous system; we await the results of this review with some eagerness. In addition, major progress has been made with respect to prospective, randomized, controlled clinical trials in breast cancer and, over the past 12 months, Dr. Kocha has initiated a pulmonary oncology group.

Dean Hollenberg of our Faculty of Medicine, has undertaken to review clinical oncology in this university to provide the basis for rationalizing and co-ordinating particularly the research and education components of cancer medicine in the City of London.

In developmental areas, Dr. Roger Inch was awarded grants by both the NCIC and the MRC to undertake a research program in nuclear magnetic resonance (NMR). Dr. Jamey Skillings was granted an award by the Ministry of Health to undertake a comparative diagnostic NMR study in patients with Hodgkin's disease and non-Hodgkin's lymphomas.

The Terry Fox training program continues to expand and, with the expertise so acquired, our monoclonal antibody group hopes to contribute new diagnostic and therapeutic measures in cancer.

This report would not be complete without mention of two major programs in the London Clinic this year. The London-Middlesex Unit of the Canadian Cancer Society and its parent — the Ontario Division, have donated approximately $750,000 towards the completion of an expanded Thameswood Lodge. This facility reopened and patients returned to the lodge in August 1983. This addition to our ambulatory-care facility will ensure the continuation of high standard health care for the large and dispersed region that we serve. In August 1983, a breast cancer screening clinic was opened in London as part of the NCIC's national study, directed by Dr. A. B. Miller. This program would not have been possible in London without the support of the Canadian Cancer Society, the Ontario Cancer Foundation and the other agencies contributing to the national program.

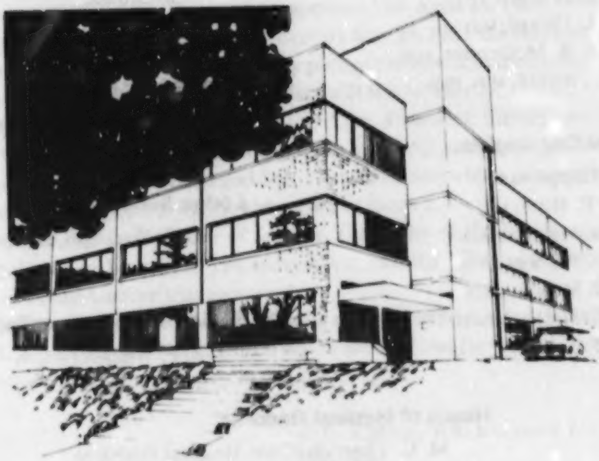
Our outreach program with St. Joseph's Hospital in London continues to mature; its starting date is the end of 1983. In addition, we continue to explore other potential outreach programs in this region.

In concluding this report it is appropriate to mention the retirement of Miss Elaine Marshall as head nurse of the clinic; Miss Marshall has served with the Ontario Cancer Foundation for some 42 years. Her years of service represent a milestone of commitment to the cause of cancer in London, and that commitment is remembered as we plan a new cancer centre for London, which will serve a large part of Southwestern Ontario for many decades to come.

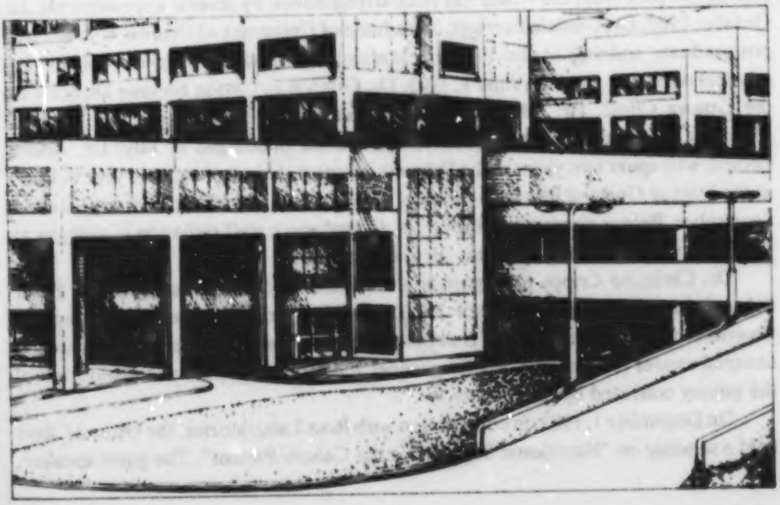
Haydn Bush, M.B., B.S., Ph.D.
F.R.C.P. (London), F.R.C.P.(C)

ONTARIO CANCER FOUNDATION OTTAWA CLINIC

OTTAWA CIVIC HOSPITAL



AND OTTAWA GENERAL HOSPITAL



Director:

G. E. Catton, M.B., B.S.

Radiation Oncologists:

A. F. Crook, M.B., B.Ch.
C. J. E. Danjoux, M.D.
L. Eapen, M.D.
A. L. Girard, M.D.
R. S. R. McDermot, M.D.
J. T. Nichol, M.D., Ph.D.

Medical Oncologists:

C. Cripps, M.D.
W. E. Hirte, M.D.
J. A. Maroun, M.D.
D. J. Perrault, M.D.
D. J. Stewart, M.D.
L. L. Stolbach, M.D.
V. P. J. Young, M.D.

Physicists:

L. H. Gerig, B.Sc.
P. M. Pfalzner, M.Sc.

Business Manager:

S. McAdam

Senior Nurse:

C. J. MacMillan, B.Sc.N.

Lodge Supervisor:

J. M. Davidson, Reg.N.

Senior Radiotherapy Technician:

R. P. Wallace, A.C.(T)

Heads of Medical Records:

M. C. Therrien (Civic Hospital Division)
M. M. Brassard (General Hospital Division)

During the past year, the Clinic has been strengthened by several appointments. In October 1982, Dr. Daniele Perrault, a graduate of University of Ottawa, who did her postgraduate training at the Princess Margaret Hospital in Toronto, joined the medical oncology staff. On June 1, 1983, Dr. Gordon E. Catton became Director of the Ottawa Clinic. Dr. Libni Eapen, who did graduate training at the Princess Margaret Hospital, joined the staff as a radiation oncologist in July. Dr. Andre Girard, who spent two years at the Princess Margaret Hospital and one year in Paris at the Institut Gustave Roussy, became a member of the radiation oncology staff in September. Before coming to Ottawa, Dr. Girard was a staff radiation oncologist at the Pavillon Carlton Auger, Hotel Dieu, Quebec City.

Dr. Christine Cripps took part in a "hot line" radio program with Dr. Peter Scholefield — Executive Director NCIC, and Mr. Brian Kennelly — Campaign Chairman of the Ottawa Carleton Unit of the Canadian Cancer Society. The discussion covered cancer treatment, Canadian cancer research programs, and disposition of the money collected by the Society.

On December 1, 1982, in conjunction with Ross Laboratories, the Ottawa Clinic held a seminar on "Nutritional Support for the Cancer Patient". The guest speaker, Dr. Hope McArdle, Assistant Director of the Surgical Clinic at the Montreal General Hospital, spoke on prophylaxis against radiation enteropathy. Local speakers gave addresses on other aspects of nutrition.

On April 30, 1983, Dr. Crook retired as staff radiation oncologist but continues on a sessional basis at the General Hospital Division.

Two centres at the Ottawa Clinic have joined the other centres across Canada to participate in the National Breast Screening Study being co-ordinated by the National Cancer Institute of Canada. This study commenced on April 26, 1983.

The CyCare computer system went "live" on May 25, 1983, the first cancer-care program to do so in Canada. At present only patient enrolment and case registration data are being computerized, scheduling data will follow shortly.

Through the Vail Visiting Professor Fund, Dr. Frederick Eilber, Professor of Surgery, UCLA, Los Angeles, came to Ottawa in May 1983, as a guest speaker at the International Symposium on Bone and Soft Tissue Tumors, which was organized by the Division of Orthopedic Surgery, University of Ottawa.

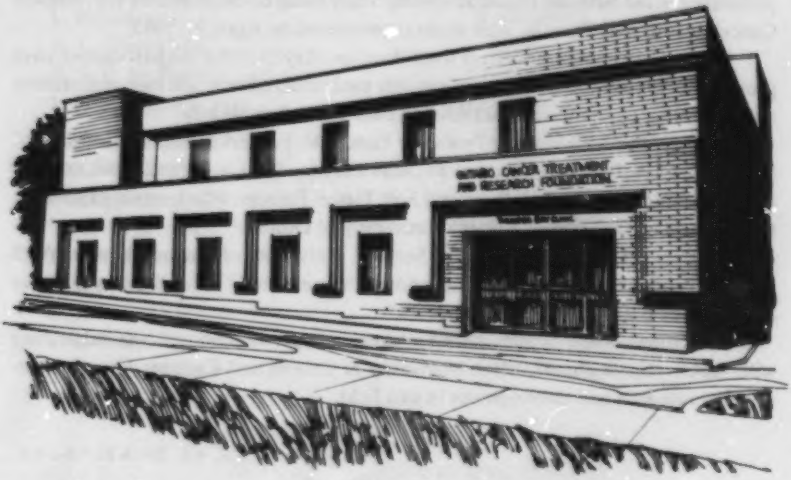
Dr. Bernard Fisher, Professor of Surgery, University of Pittsburgh, was a Vail Visiting Professor in June 1983. His address was entitled "Role of Science in the Evolution of Breast Cancer Management".

The Ottawa Clinic is pursuing its interest in hyperthermia and is collaborating with AECL (Chalk River), NRC, University of Ottawa and Carleton University in ongoing research and development in this field.

G.E. Catton, M.B., B.S., D.M.R.T., F.R.C.P.(C)
Director

ONTARIO CANCER FOUNDATION THUNDER BAY CLINIC

GENERAL HOSPITAL OF PORT ARTHUR


ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION

Director:
J. F. Kotalik, M.D.

Radiation Oncologists:
W. A. Hargan, M.D.
F. H. W. Hellmuth, M.D.

Medical Oncologist:
M. D. E. Goodyear, M.B., B.S.

Clinical Assistant:
J. A. Chalykoff, M.D.

Physicist:
P. D. Sharma, M.Sc.

Business Manager:
M. M. Ryan

Senior Nurse:
L. Bright, Reg.N.

Supervisory Radiotherapy Technician:
J. V. Morgan, R.T.

Nurse Social Worker:
V. Coley, Reg.N.

Head of Medical Records:
M. P. Winfield, C.C.H.R.A.(A)

Lodge Supervisor:
B. C. Petty

1983 was not only an anniversary year for the Foundation but also in this year our clinic celebrated its 35th Anniversary. Our program started in the spring with a special lecture organized in co-operation with the Thunder Bay Medical Society and attended by most of the physicians of the city. Dr. W. M. Hryniuk, Director of the Hamilton Clinic, discussed the medical management of carcinoma of the breast, with special emphasis on pain control. A luncheon honoring the Canadian Cancer Society's volunteers and volunteer drivers was held at Amethyst House. Later in September an anniversary dinner was attended by the Chairman, Mr. Michael A. Meighen, Dr. J. W. Meakin and Mr. R. D. Gray. Dr. W. A. Hargan reviewed the early history of our clinic and Mr. R. J. Prettie presented long-service awards to some members of our staff. Subsequently, we held an Open House and many members of the community came to see the exhibits and demonstrations which each of the departments had prepared. A special Open House for the media and press conference were held to inform the public about our past achievements and future goals. A documentary film about our clinic is being produced by MacLean Hunter Cable T.V., a local television station.

Space is at a premium in our clinic and earlier we made some minor renovations to accommodate our computer equipment and to create a room for the counselling of patients. Our staff is being trained in the many uses of the computer and we look forward to a time of increased efficiency and more reliable data.

A new radiotherapy planning computer is now in operation with software which will allow us to use magnetic tape from the EMI CT scanner at McKellar General Hospital. This scanner is now available in designated times for radiotherapy planning by our own staff.

Our major equipment need remains the high-energy linear accelerator and our host hospital is actively supporting our efforts to obtain this essential treatment unit.

On July 1, Dr. F. H. W. Hellmuth joined our staff as a full-time radiation oncologist. He came from the Manitoba Cancer Treatment and Research Foundation.

Dr. Michael Goodyear was appointed Medical Oncologist in our Clinic. This joint appointment with the Hamilton Clinic allows us to develop our clinical trials program and maintain close co-operation with our sister clinic. We are continuing our effort to recruit further medical oncologists. In the meantime, we have been able to maintain and develop our chemotherapy program with the help of locum medical oncologists and trainees from the Princess Margaret Hospital in Toronto. During the past year, the following physicians served in this capacity: Drs. Brian Norris from Vancouver, Alexander Paterson from Edmonton, and John Ford from Toronto. Locum radiation oncologists who served this clinic from January until the end of June were: Drs. Curtis Johanson from Toronto, Lois Myers from the United Kingdom, and Uma Monga from Kingston. We are most grateful for their assistance.

J. F. Kotalik, M.D., D.M.R.T., F.R.C.P.(C)
Director

ONTARIO CANCER FOUNDATION TORONTO-BAYVIEW CLINIC

SUNNYBROOK MEDICAL CENTRE

Director:

R. D. T. Jenkin, M.B., B.S.

Radiation Oncologists:

M. P. Berry, M.B., B.S.
P. A. Catton, M.D.
R. G. MacKenzie, M.D.

Medical Oncologists:

N. Iscoe, M.D.
I. J. Kerr, M.D.
D. Osoba, M.D.
J. J. Rusthoven, M.D.
D. J. A. Sutherland, M.D.

Clinical Assistants:

H. M. Kocandrle, M.D.
T. B. McQuiston, M.D.

Physicists:

H. B. Michaels, Ph.D.
P. F. O'Brien, M.Sc.
R. A. Siwek, Ph.D.

Business Manager:

L. D. Langdon, M.H.A.

Senior Nurse:

C. Johnston, Reg.N.

Senior Radiotherapy Technician:

A. Bissett, R.T.(T)

Head of Medical Records:

M. Mistruzzi, C.C.H.R.A.(C)

1983 has been a very active year at the Toronto-Bayview Clinic. The major increase of staff accomplished during the previous year proved just adequate to manage our increasing patient population. New patient referrals increased by 50% to a rate of 1850 per year by year's end, compared to 1250 per year one year earlier. The current exponential rate of increase in our new patient referrals suggest that our planned capacity of 2500 patients per year will by reached by May 1984. Therefore all departments are having to consider expansion plans. During the year our total clinic staff increased by 25% to 78.

Our in-patient activity at Sunnybrook Medical Centre's Department of Oncology increased proportionally with our out-patient growth, 55 beds compared to 36 one year earlier. In October, 36 of these beds moved from an old section of the hospital to the newly constructed C-wing, which also houses the "radium" room and operative suites, which will be used for diagnostic and radiation oncological procedures.

This overall expansion was reflected by sharply increased activity in each department. In clinical physics, Dr. Rosemarie Siwek joined the staff and the primary effort went into commissioning the 6 MeV linear accelerator early in the year and the 25 MeV accelerator by year's end. A ceremony, held on June 14, 1983, to celebrate the commissioning of the 25 MeV accelerator, was chaired by Mr. Michael Meighen and included presentations by the Honorable Larry Grossman — Minister of Health, Mr. Ian Douglas — Chairman of the Board of Trustees at Sunnybrook Medical Centre, and Mr. R. A. Harrod from Atomic Energy of Canada Ltd.

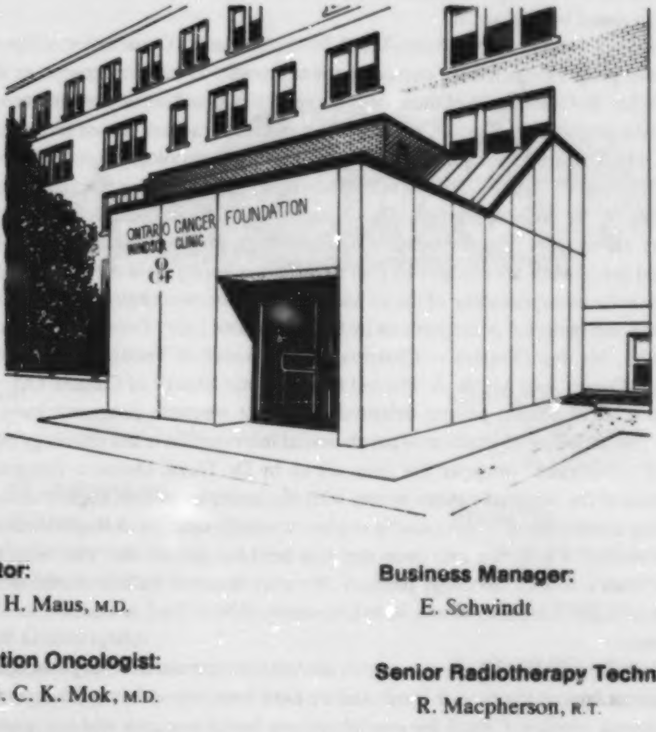
In clinical affairs, patient-oriented treatment research programs have been developed including evaluation of psychosocial intervention in the oncology patient. A pilot "cancerlink" program has been set up by Dr. David Osoba to integrate the functions of the regional cancer centre with the activities of oncologists within our referring constituency — necessarily the latter usually operate as single individuals. In November, a program and open day was held for physicians, who refer to the centre head and neck oncology patients. We were honored on that occasion by the presence of Dr. John Lore of the State University of New York at Buffalo, as visiting professor.

Unfortunately our inhouse research laboratories remain as empty space, due to the current famine in research funds and we have been dependent on the support of Sunnybrook Medical Centre for our laboratory-based research and for space and equipment. Thus our chief unfulfilled goal remains the development of a research division within the clinic.

R. D. T. Jenkin, M.B., B.S.
Director

ONTARIO CANCER FOUNDATION WINDSOR CLINIC

METROPOLITAN GENERAL HOSPITAL



ONTARIO CANCER FOUNDATION
WINDSOR CLINIC
OCF

Director:
J. H. Maus, M.D.

Radiation Oncologist:
G. C. K. Mok, M.D.

Medical Oncologists:
H. T. Abu-Zahra, M.B., B.Ch.
D. B. McDonald, M.D.
S. Yoshida, M.D.

Physicist:
D. Smocovitis, M.Sc.

Business Manager:
E. Schwindt

Senior Radiotherapy Technician:
R. Macpherson, R.T.

Senior Nurses:
A. Beaton, Reg.N.
M. O'Neill, Reg.N.

Head of Medical Records:
V. L. Gignac

1983 has been a year of consolidation following completion of our structural additions. Our experience over the current year has been satisfying with respect to the use of our new space. It appears that the plans we made to take over the first floor of Metropolitan Hospital just above the Clinic for our Medical Oncology Division and the addition of a fine, new library will benefit our staff and our patients for the foreseeable future. The staff of the Clinic have continued to follow protocols of the National Cancer Institute of Canada and of the Southwest Oncology Group. Our associations with these two organizations give us an opportunity to update our medical knowledge and, in the long term, this will be reflected in better patient care. In 1983 we installed our new computer and it is now part of the network of the OCTRF's Information Systems. Our cases are being entered on the computer and we are exploring the various capacities of the new system, both in terms of patient registration and patient scheduling. We look forward to increasing benefits, particularly in patient registration and hope to be able to assess the results of treatment once the computer system is fully in place. Demands for service — both from radiation oncology and medical oncology, continue to mount and we look forward to some additions to our staff at an early date. Fiscal restraints are of great concern as we struggle to balance our various budgets but like the other clinics, we continue to meet demands for the service with the existing staff. We record with gratitude the assistance of the volunteers of the Canadian Cancer Society, Ontario Division, and the Essex County District in particular and the help of the Hospice of Windsor in dealing with the emotional adjustments following the appearance of cancer in the family. In particular our three medical oncology physicians have contributed their time and knowledge to the Hospice in an advisory capacity. This facility also is a valuable vehicle of volunteer assistance to both patients and family during the period of illness associated with malignant disease.

J. H. Maus, M.D.
Director

SERVICE LOAD

The following five tables describe the service load of the regional treatment centres associated with the Foundation during the calendar year 1982. On January 1, 1982, with the implementation of the Patient Care Management System in the treatment centres it has been possible to retrieve data in more detail than was possible in previous years. However, the system was not implemented as rapidly as initially planned and the tabulations are marked "Provisional" because of some discrepancies which are being corrected. Also it must be emphasized that these tables are not comparable with the service load tables published for previous years, and also are not comparable with the data for the fiscal year for the Princess Margaret Hospital. If compared with previous years, numbers in these tables show a marked increase but this is due to a better estimate of service load as well as to some real increase. In subsequent years, our reports will follow the format and definitions used in these tables.

In 1982, 39,422 patients were seen at the Foundation treatment centres. Malignant lesions accounted for 93% and, of these, 10,266 were new to the clinics (Table I). In Table II it should be noted that only 68 non-malignant cases were registered in any previous year compared with almost 1,500 in 1981 (total — 2,966 less 1,666 from PMH equals 1,500; now and in the future, PMH case load data will be shown separately). This is due to one of the changes in the definitions used, the new definition recognizes that a patient seen in a previous year with cancer and presenting with a benign condition in 1982, will also be assessed for the cancer at the same time. Seven thousand and twenty-five cancer cases were treated by radiotherapy of whom 3,619 (51.5%) were treated by cobalt^{60} units (Table III).

During the year, patients made 347,394 visits to the regional treatment centres and the majority (16,294) were made by cancer patients for treatment with radiation (Table IV). Twenty-one per cent of these treatments were given to out-patients (Table V).

TABLE I*

Malignant Caseload During 1982[1]

TREATMENT CENTRE	TREATED				SEEN FOR CONSULTATION OR FOLLOW-UP	TOTAL
	Radiation	Radiation and Chemotherapy	Chemotherapy and/or Immunotherapy	Other		
	Cases New in Current Year					
Hamilton	1,060	129	368	29	875	2,461
Kingston	519	43	52	25	377	1,016
London	1,114	113	152	168	701	2,248
Ottawa	768	172	361	107	852	2,260
Thunder Bay	178	40	47	—	185	450
Toronto-Bayview	251	80	113	83	401	928
Windsor	293	64	196	17	333	903
TOTAL	4,183	641	1,289	429	3,724	10,266
	Cases Registered in any Previous Year					
Hamilton	391	171	781	46	4,326	5,715
Kingston	199	49	156	39	2,446	2,889
London	304	130	323	347	5,487	6,591
Ottawa	297	241	894	140	5,089	6,661
Thunder Bay	83	44	144	1	933	1,205
Toronto-Bayview	25	45	111	18	383	582
Windsor	69	60	417	7	2,136	2,689
TOTAL	1,368	740	2,826	598	20,800	26,332
TOTAL ALL MALIGNANT	5,551	1,381	4,115	1,027	24,524	36,598

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* Provisional (transition period — see text)

[1] Includes cases seen at peripheral clinics.

TABLE II*

Other (Non-Malignant) Caseload During 1982[1]

TREATMENT CENTRE	TREATED				SEEN FOR CONSULTATION OR FOLLOW-UP	TOTAL
	Radiation	Radiation and Chemotherapy	Chemotherapy and/or Immunotherapy	Other		
	Cases New in Current Year					
Hamilton	32	—	35	12	242	321
Kingston	18	—	9	67	248	342
London	89	—	20	393	611	1,113
Ottawa	7	1	3	168	69	248
Thunder Bay	25	—	—	1	116	142
Toronto-Bayview	3	—	—	180	203	386
Windsor	8	2	18	1	175	204
TOTAL	182	3	85	822	1,664	2,756
	Cases Registered in any Previous Year					
Hamilton	1	—	1	—	5	7
Kingston	1	—	—	—	10	11
London	—	—	—	3	8	11
Ottawa	—	—	—	—	7	7
Thunder Bay	—	—	—	—	2	2
Toronto-Bayview	1	—	—	7	17	25
Windsor	1	—	—	—	4	5
TOTAL	4	—	1	10	53	68
TOTAL OTHER	186	3	86	832	1,717	2,824

* Provisional (transition period — see text)

[1] Includes cases seen at peripheral clinics.

TABLE III*

Cases Treated During 1982 by Method of Radiotherapy

METHOD OF TREATMENT	HAMILTON	KINGSTON	LONDON	OTTAWA	THUNDER BAY	TORONTO BAYVIEW	WINDSOR	TOTAL
	Malignant Neoplasms							
Superficial x-ray	344	146	115	16	34	4	—	659
Deep x-ray	39	15	—	—	12	6	100	172
Cobalt^{60}	963	323	524	811	294	332	372	3,619
Cesium^{137}	—	—	2	—	—	—	—	2
Betatron	—	—	281	—	—	—	—	281
Linear accelerator	362	314	576	624	—	65	—	1,941
Intracavitary	60	21	119	40	14	1	33	288
Interstitial	1	7	30	—	4	8	—	50
Moulds and applicators	—	—	11	—	—	—	—	11
Systemic isotopes	—	1	—	—	—	—	—	1
Others	—	—	1	—	—	—	—	1
SUB-TOTAL	1,769	827	1,659	1,491	358	416	505	7,025
	Other Non-Malignant							
Superficial x-ray	23	8	60	—	21	—	—	112
Deep x-ray	—	—	—	—	1	1	3	5
Cobalt^{60}	6	8	11	4	3	2	6	40
Cesium^{137}	—	—	—	—	—	—	—	—
Betatron	—	—	3	—	—	—	—	3
Linear accelerator	2	3	13	4	—	1	—	23
Intracavitary	—	—	—	—	—	—	—	—
Interstitial	—	—	2	—	—	—	—	2
Moulds and applicators	—	—	—	—	—	—	—	—
Systemic isotopes	—	—	—	—	—	—	—	—
Others	—	—	4	—	—	—	—	4
SUB-TOTAL	31	19	93	8	25	4	9	189
TOTAL[1]	1,800	846	1,752	1,499	383	420	514	7,214

* Provisional (transition period — see text)

[1] A case can be treated by more than one method per year.

TABLE IV*

Service Load, 1982

TREATMENT CENTRE	VISITS FOR					TOTAL VISITS
	Treatment			Non-Treatment		
	Radiation	Chemotherapy Immunotherapy	Other	Simulation	*Consultation or Follow-up*	
			Visits for Malignant Neoplasms			
Hamilton	27,271	9,886	819	3,057	31,437	72,470
Kingston	13,577	1,289	411	1,450	13,815	30,542
London	28,816	3,772	1,734	3,725	29,617	67,664
Ottawa	25,514	13,523	1,060	2,043	45,855	87,995
Thunder Bay	7,073	1,774	115	435	7,285	16,682
Toronto-Bayview	4,327	2,386	265	716	13,872	21,566
Windsor	9,716	6,776	363	872	24,076	41,803
TOTAL	116,294	39,406	4,767	12,298	165,957	338,722
			Other Non-Malignant			
Hamilton	115	72	156	38	805	1,186
Kingston	185	8	231	26	540	990
London	376	39	1,175	125	1,922	3,637
Ottawa	118	9	460	9	174	770
Thunder Bay	95	2	23	9	305	434
Toronto-Bayview	53	2	214	5	715	989
Windsor	147	48	26	11	434	666
TOTAL	1,089	180	2,285	223	4,895	8,672
TOTAL ALL VISITS	117,383	39,586	7,052	12,521	170,852	347,394

*Provisional (transition period — see text)

TABLE V*

Treatments by Radiation During 1982, In-Patients and Out-Patients

METHOD OF TREATMENT	HAMILTON		KINGSTON		LONDON		OTTAWA		THUNDER BAY		TORONTO BAYVIEW		WINDSOR		TOTAL	
	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out
								Malignant Neoplasms								
Superficial x-ray	7	1,812	32	661	—	503	14	74	8	186	—	63	—	—	61	3,299
Deep x-ray	75	292	43	113	—	—	—	—	26	135	—	89	29	1,619	173	2,248
Cobalt^{60}	2,302	12,749	1,785	4,484	3,058	8,487	2,894	10,917	1,010	5,515	736	4,941	959	6,986	12,744	54,079
Cesium^{137}	—	—	—	—	89	46	—	—	—	—	—	—	—	—	89	46
Betatron	—	—	—	—	747	5,094	—	—	—	—	—	—	—	—	747	5,094
Linear accelerator	915	7,175	957	6,005	2,682	6,994	1,281	10,062	—	—	138	1,565	—	—	5,973	31,801
Intracavitary	83	—	27	—	140	—	52	—	22	—	1	—	45	—	370	—
Interstitial	—	1	—	7	13	19	—	—	4	—	—	9	—	—	17	36
Moulds and applicators	—	—	—	—	2	10	—	—	—	—	—	—	—	—	2	10
Systemic isotopes	—	—	1	—	—	—	—	—	—	—	—	—	—	—	1	—
Others	—	—	—	—	—	4	—	—	—	—	—	—	—	—	—	4
SUB-TOTAL	3,382	22,029	2,845	11,270	6,731	21,157	4,241	21,053	1,070	5,836	875	6,667	1,033	8,605	20,177	96,617
METHOD OF TREATMENT								Other Non-Malignant								
Superficial x-ray	—	38	4	16	—	73	—	—	—	58	—	—	—	—	4	185
Deep x-ray	—	-	—	—	—	—	—	—	—	15	—	9	—	11	—	35
Cobalt^{60}	4	25	22	86	36	38	23	22	3	45	24	20	40	96	152	332
Cesium^{137}	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Betatron	—	—	—	—	10	24	—	—	—	—	—	—	—	—	10	24
Linear accelerator	48	—	2	55	41	113	10	53	—	—	—	25	—	—	101	246
Intracavitary	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Interstitial	—	—	—	—	—	2	—	—	—	—	—	—	—	—	—	2
Moulds and applicators	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Systemic isotopes	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Others	—	—	—	—	—	19	—	—	—	—	—	—	—	—	—	19
SUB-TOTAL	52	63	28	157	87	269	33	75	3	118	24	54	40	107	267	843
TOTAL OF ALL TREATMENTS	3,434	22,092	2,873	11,427	6,818	21,426	4,274	21,128	1,073	5,954	899	6,721	1,073	8,712	20,444	97,460

* Provisional (transition period — see text)

ONTARIO CANCER INSTITUTE

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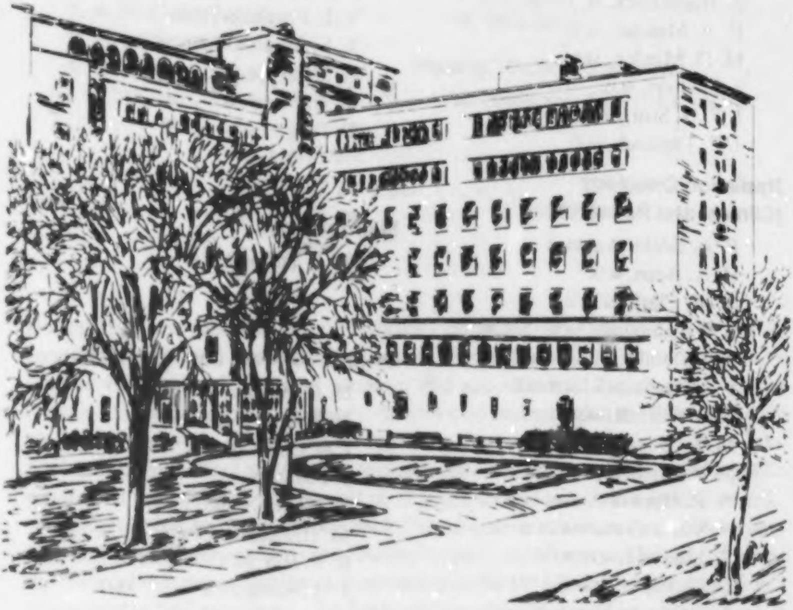
PRINCESS MARGARET HOSPITAL



Director:
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Medical Oncology (Clinical and Research):

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C. Erlichman, M.D.
R. Feld, M.D.
S. Fine, M.D.
R. Hasselback, M.D., C.M.
H. A. Messner, M.D.
M. D. Minden, M.D.
I. C. Quirt, M.D.
J. F. G. Sturgeon, M.B., B.S.
I. F. Tannock, M.D.

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P. J. Fitzpatrick, M.B., B.S.
P. G. Garrett, M.D.
M. K. Gospodarowicz, M.D.
M. A. Gribbin, M.B., B.S.
A. R. Harwood, M.B., Ch.B
N. V. Hawkins, M.B., B.S.
T. J. Keane, M.B., B.Ch.
D. G. Payne, M.D.
J. F. Pringle, M.B., Ch.B.
G. A. Rawlings, M.D.
W. D. Rider, M.B., Ch.B.
W. J. Simpson, M.D.
S. B. Sutcliffe, M.D.
G. M. Thomas, M.D.

Diagnostic Radiology:

R. Blend, M.B., B.S.
S. Herman, M.D.
I. F. Majesky, M.D.
P. Y. Poon, M.B., B.S.
D. F. Rideout, M.B., B.S.

Nuclear Medicine:

G. N. Ege, M.D.
J. L. Yeoh, M.D.

Pathology:

C. Bergeron, M.D.
T. C. Brown, M.D.
J. S. Carruthers, M.D.
V. L. Fornasier, M.D.
A. E. Kossakowska, M.D.
G. J. Laroye, M.D.
M. E. Platts, M.D.
T. Treger, M.D.

Microbiology:

P. G. Tuffnell, M.D.

Physics (Clinical and Research):

M. C. Archer, Ph.D.
M. J. Bronskill, Ph.D.
J. R. Cunningham, Ph.D.
S. Foster, Ph.D.
D. M. Galbraith, B.Sc.
M. Henkelman, Ph.D.
R. P. Hill, Ph.D.
J. W. Hunt, Ph.D.
B. Japp, B.Sc.
P. M. K. Leung, Ph.D.
H. Maharaj, B.Sc.
A. Mosseri, M.Sc.
P. N. Munro, M.Sc.
F. P. Ottensmeyer, Ph.D.
A. M. Rauth, Ph.D.
A. J. Rawlinson, M.Sc.
W. B. Taylor, B.Eng.
J. Van Dyk, M.Sc.
H. P. Webb, C.E.T.
G. F. Whitmore, Ph.D.

Biological Research:

S. Benchimol, Ph.D.
A. Bernstein, Ph.D.
R. Buick, Ph.D.
A. Ciampi, Ph.D.
A. J. Cunningham, Ph.D.
R. M. Gorczynski, Ph.D.
N. Hozumi, Ph.D.
V. Ling, Ph.D.
T. W. Mak, Ph.D.
E. A. McCulloch, M.D.
R. G. Miller, Ph.D.
R. A. Phillips, Ph.D.
J. E. Till, Ph.D.

Biostatistics:

G. DeBoer, Ph.D.
D. Tritchler, Ph.D.

Administrator:

J. E. Ratz

Assistant Administrators:

T. Brazier
J. P. Holder, Reg.N.
T. J. D. West
W. Wilkinson

Head of Medical Records:

A. Buchanan, B.A., C.C.H.R.A.(C)

Librarian:

C. Morrison, B.A., M.L.S.

During 1983, the Ontario Cancer Institute celebrated the 25th anniversary of its opening in 1958. Sixty former residents from all over the world returned to attend a reunion consisting of a lecture program and special social functions. A similar reunion was held for the postdoctoral fellows who had attended the Department of Medical Biophysics and Biological Research. A reunion also was held for the graduates of the school of radiation technologists. An open weekend for the public was a great success and veteran staff of 25 years service received a special award.

The Hospital and Institute look back on one-quarter of a century of achievement in research and quality patient care. During the year, the Ministry of Health informed the Institute that the expansion recommended in the 1973 Role Study and approved in principal in 1981 could not be funded in the immediate future. This setback has left the Department of Radiation Oncology poorly provided for, particularly with regard to treatment machines. A 6 MeV linear accelerator has replaced two of the department's historic cobalt units — the "Xotron" and the "Double Header" and next year a new 25 MeV linear accelerator will replace the venerable betatron. These machines will materially improve the range and quality of treatment offered by the department but will not increase the number of machines available for treatment.

There has been no staff changes in the Department of Medical Oncology but the Department of Radiation Oncology regrets to announce the departure of Dr. J. Herman. Drs. A. E. Kossakowska and C. Bergeron have joined the Department of Pathology. Dr. S. Benchimol has become a member of the Department of Biological Research. Pauline Jackson has been appointed Public Relations Officer.

A prototype NMR (nuclear magnetic resonance) imager, which was installed this year, was provided by a grant from the Ministry of Health; a program for clinical evaluation has started. NMR employs a completely new principal of imaging and we hope that it will be particularly useful for the imaging of soft tissue structures and so lead to better tumor definition and localization. Further progress has been made in ultrasound imaging and, in particular, an instrument has been developed for breat tumor imaging, which incorporates a new transducer principle; the prototype will be tested at the Institute and the Women's College Hospital.

In addition to its work in clinical imaging, the OCI has made advances in imaging at the subcellular level, which assists our work in molecular biology. These are exciting times for the molecular biologist: after nearly 30 years of effort, new discoveries are being made concerning the structure of the DNA molecule (during the year, the complete structure for the DNA of a leukemogenic virus was determined at the OCI), and concerning to transcription by RNA. New techniques of genetic manipulation promise to elucidate fundamental principals of tumor formation and eventually may make it possible to correct cellular genetic defects.

Of more immediate clinical importance, recent work on hemopoiesis suggests that some, though not all, stem cells can give rise to lymphocytes. A new cell type ("veto" cell) has been identified, which has the capacity to delete certain lymphocyte precursors that are capable of recognizing normal cells. These "veto" cells may be important in the maintenance of cellular self-identity by the system. New immunological reagents have identified doubly marked cells, which respond poorly to chemotherapy; such information is useful in the planning of trials and in individualizing treatment regimens. In addition, a specific cell-surface protein appears to be important in determining the response of tumor cells to anticancer drugs.

The resistance to drugs of many types of human tumors is being investigated using solid tumor nodules (spheroids) grown in tissue culture. It is postulated that the failure to respond to some anticancer drugs mimics the known decreased radiosensitivity of anoxic tumor cells and that if these drugs were combined with others without oxygen dependence we could develop more effective drug combinations. The development of drugs effective against the hypoxic tumor cell would greatly facilitate the rational combination of radiation and chemotherapy.

The work on hypoxic-cell sensitisers to radiation continues in four experimental fields: At the metabolic level, at the in vitro level of mammalian cells tissue culture, with in vivo mouse tumor systems, and with clinical trials in patients. While these studies are progressing, a serendipitous discovery — the effectiveness of 5-fluorouracil and mitomycin C with radiation for squamous-cell carcinoma of the anal canal, is being systematically investigated for tumors of the larynx, esophagus and cervix. With such encouraging clinical results, it is to be hoped that appropriate experimental studies will be started in the laboratory. If further studies elucidate the method of action of these drugs, we can anticipate further advances in the application of adjuvant chemotherapy to radiation.

DNA repair processes play a critical role in determining the outcome when a tumor is exposed to irradiation and chemotherapeutic agents. Certain individuals, who because of rare genetic disease lack such repair processes, are exquisitely sensitive to damage from these agents. When a human repair gene is transferred into repair-deficient Chinese hamster cells, it converts the recipient cells from a state of extreme sensitivity to ultraviolet light and mitomycin C to a state of essentially normal resistance. This is the first step in an attempt to clone the human gene and the isolation of the human DNA responsible for repair will enable us to study it in detail. Thus the investigation of DNA is of fundamental importance not only in the elucidation of the mechanisms of carcinogenesis but also to an understanding of treatment.

In addition to clinical studies with 5-fluorouracil and mitomycin C and the hypoxic-cell sensitisers mentioned above, studies are underway in carcinoma of the breast, malignant melanoma, myeloma, malignant lymphoma, carcinoma of the lung, ovary, nasopharynx, testis, prostate and rectum. Four trials are underway in breast cancer: A comparison of chemotherapy alone with chemotherapy and ovarian ablation in the adjuvant treatment of premenopausal women, a comparison of tamoxifen as an adjuvant treatment without postoperative irradiation in postmenopausal women, and two trials in patients with metastatic breast cancer. Three studies have been done in malignant melanoma, and studies in multiple myeloma and malignant lymphoma continue. The OCI continues to be active in co-operative international trials in small-cell carcinoma of the lung and ongoing investigative programs are progressing for treatment of carcinoma of the ovary and testis. A controlled trial of adjuvant chemotherapy in carcinoma of the nasopharynx is nearing completion.

The expanded dental service is providing valuable support to patients undergoing treatment particularly for head and neck cancer and is proving cost effective. Nursing and nutritional support has also proved to be of great benefit to these patients and has made it possible to treat many of them outside the hospital.

At last some notice is being taken of the poor state of undergraduate teaching in oncology at the University of Toronto. In a survey of all Canadian medical schools, the University of Toronto ranked among the least adequate. It is to be hoped that the Curriculum Committee will act to improve this teaching. In 1982-83, 16 undergraduates were taking electives at the Princess Margaret Hospital, 13 from Toronto and 3 from other Canadian universities.

While the neglect of undergraduate teaching continues, postgraduate training in oncology is improving. The Ministry of Health has funded three additional resident posts in radiation oncology raising the total to 17. The OCTRF funded two more posts in medical oncology raising the total to 11. There also are six residents in the Department of Pathology. In addition to residents, there are five clinical fellows in radiation oncology and three research fellows in the Department of Medicine. The Terry Fox Training Program for postdoctoral fellows continues to attract applicants from all over the world. Since the program's inception, five Terry Fox fellows have taken up their awards, three of these are still actively engaged in their projects; an additional 11, who have been awarded fellowships, will begin their research during the coming year. The Department of Medical Biophysics continues to attract first-rate graduate students. During the past year, 26 postdoctoral fellows received further research experience, and 37 graduate students are working in the various laboratories — three of these have completed the Ph.D. degree and three the M.Sc. degree

Ten new students have been accepted into the School of Radiotherapeutic Technology raising the total in training to 18. Eleven other students are attending the didactic portion of the program from other centres in Ontario and Canada.

The Department of Nursing has developed programs designed to support staff in their role as oncology nurses. Seventy nursing students from the Durham College spent three days at the hospital and 100 students from other community colleges attended for one-half day sessions.

In June, Dr. R. Clark organized a highly successful symposium on carcinoma of the breast which was attended by 225 participants. Drs. S. Sutcliffe and T. Brown are developing a laboratory for phenotyping and karyotyping lymphoma cells.

This year the number of bone-marrow transplants passed the one-hundred mark. Over one-half of the patients transplated since 1979 are alive and free of their original disease although subsequent graft-versus-host disease and late infections continue to be a problem. While limited facilities restrict the number of transplants we can perform, the demand for this procedure is increasing. Results continue to improve and late relapse of the original disease is rare.

During the year Dr. E. A. McCulloch was promoted to the position of University Professor. The Institute received the Bristol-Myers award for innovative and unrestricted cancer research. The award is worth $500,000 spread over five years.

N. V. Hawkins, M.B., B.S., D.M.R.T., F.R.C.P.(C)
Radiation Oncologist

TABLE VI*

Pediatric Cases Under 17 Years of Age Treated at PMH
April 1982 — March 1983

Leukemia	40
Lymphomas:	
Hodgkin's disease	11
Non-Hodgkin's lymphoma	8
Bone tumors:	
Ewing's sarcoma	3
Sarcomas:	
Rhabdomyosarcoma	6
Other sarcomas	2
CNS:	
Medulloblastoma	9
Ependymoma	4
Astrocytoma	3
Other gliomata	2
Other NCS tumors	6
Neuroblastoma	12
Nephroblastoma	9
Retinoblastoma	7
Other malignant neoplasms	11
Benign and non-neoplastic lesions	15
TOTAL	148

*Reprinted, with permission, from the Ontario Cancer Institute's Annual Report for 1982-1983.

TABLE VII*

Number of Treatments Given in the PMH Department of Radiotherapy April 1982 — March 1983

EXTERNAL BEAM	
Superficial x-ray	1,815
Deep x-ray	2,743
Cobalt	48,556
Cesium	74
Betatron	5,854
Linear accelerator	24,365
TOTAL	83,407
Inpatient treatments	16,938
Outpatient treatments	66,469
TOTAL	83,407
SEALED SOURCES	
Intracavitary	258
Interstitial (needles, wires, seeds and grains)	57
Moulds and applicators	100
TOTAL	415

*Reprinted, with permission, from the Ontario Cancer Institute's Annual Report for 1982-1983.

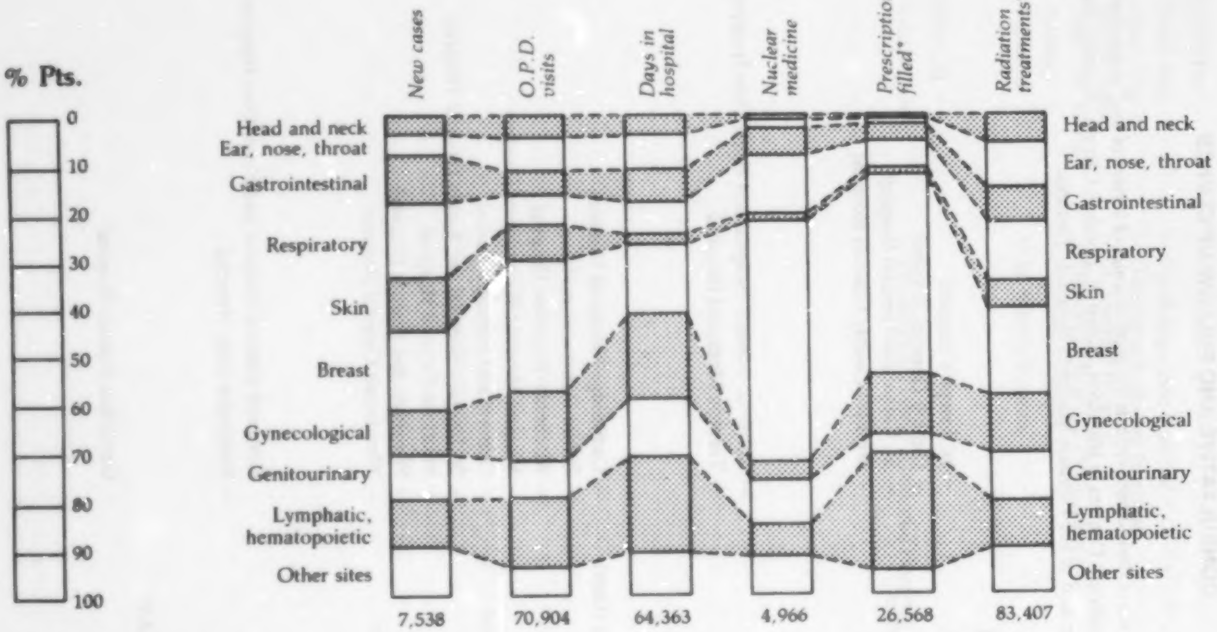
TABLE VIII*

Services Provided by PMH at Peripheral Clinics April 1982 — March 1983

CLINIC	NEW PATIENTS SEEN		PERIPHERAL CLINIC VISITS**	
	Malignant	Other	Malignant	Other
North Bay	124	7	1,289	35
Owen Sound	82	3	691	24
Peterborough	27	–	1,583	58
Sault Ste. Marie	51	2	775	13
Sudbury	32	–	1,227	32
Timmins	32	7	1,016	35
TOTAL	348	19	6,581	197

*Reprinted, with permission, from the Ontario Cancer Institute's Annual Report for 1982-1983.

**Including the visits when patients are first seen at peripheral clinics as well as subsequent visits for new and old patients.



*Chemotherapy only

†External beam only

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Fig. 1. Princess Margaret Hospital workload by site of disease, expressed as a percentage of workload, April 1982-March 1983.

CONSULTATIVE AND FOLLOW-UP CLINICS

The distribution of these clinics reflects the general zones of service of the Foundation's Regional Treatment Centres in Hamilton, Kingston, London, Ottawa, Thunder Bay and Windsor; and of the Princess Margaret Hospital, Toronto.

HAMILTON

Brantford – St. Joseph's Hospital
Guelph – Guelph General Hospital
St. Catharines – St. Catharines General Hospital
Welland – Welland County General Hospital

KINGSTON

Cornwall -- Cornwall General Hospital and Hotel Dieu Hospital
Trenton – Trenton Memorial Hospital

LONDON

Cambridge (Galt) – Cambridge Memorial Hospital
Chatham – Public General Hospital
Kitchener – Kitchener-Waterloo Hospital
London – Victoria Hospital Westminster Campus
Owen Sound – General and Marine Hospital
Sarnia – St. Joseph's Hospital and Sarnia General Hospital
Stratford – Stratford General Hospital
Wingham – Wingham and District Hospital
Woodstock – Woodstock General Hospital

OTTAWA

Cornwall – Cornwall General Hospital and Hotel Dieu Hospital
Pembroke – Pembroke Civic Hospital

THUNDER BAY

Geraldton – Geraldton District Hospital

TORONTO

North Bay – North Bay Civic Hospital
Owen Sound – General and Marine Hospital
Peterborough – St. Joseph's Hospital
Sault Ste. Marie – Plummer Memorial Public Hospital
Sudbury – Laurentian Hospital
Timmins – St. Mary's Hospital

WINDSOR

Leamington – Leamington District Memorial Hospital

CLINICAL CONSULTANTS AT ONTARIO CANCER FOUNDATION CLINICS AND THE PRINCESS MARGARET HOSPITAL

(As at December 31, 1983)

OCF Hamilton Clinic:

M. Ali, M.D.
S. Archibald, M.D.
H. W. Beattie, M.D.
A. M. Benger, M.D.
W. F. Bennett, M.D.
I. W. Blackstone, M.D.
M. Brain, M.D.
B. Clark, M.D.
D. Clark, M.D.
I. R. Davis, M.D.
P. B. Dent, M.D.
A. D. DePetrillo, M.D.
J. D. Gowing, M.B., B.S.
M. Gross, M.D.
R. A. Hadden, M.D.
D. A. Hitch, M.D.
G. K. Ingham, M.D.
B. S. Jackson, M.D.
P. Jenkin, M.D.
J. Kearns, M.D.
P. Knight, M.B., Ch.B.
G. A. Lane, M.D.
E. J. Latimer, M.D.
J. A. McBride, M.B., Ch.B.
S. E. O'Brien, M.D.
G. O'Connell, M.D.
W. L. Orovan, M.D.
J. T. Roberts, M.B., Ch.B.
D. Rosenthal, M.D.
D. Sauder, M.D.
B. Trossman, M.D.
P. Vasarinsh, M.D.
I. Walker, M.D.
W. E. C. Wilson, M.D.
C. Woolever, M.D.
J. E. M. Young, M.D.

OCF Kingston Clinic:

J. M. Blakeman, M.D.
J. A. Carmichael, M.D.
W. E. N. Corbett, M.D.
D. Dexter, M.D.
S. F. Hall, M.D.
J. W. Kerr, M.D.
K. W. Mackie, M.D.
J. R. McCorriston, M.D.
R. J. Riopelle, M.D.
D. M. Robertson, M.D.
H. D. Steele, M.D.
E. E. Sterns, M.D.
K. Taguchi, M.D.
D. M. L. Williams, M.D.

OCF London Clinic:

H. H. Allen, M.D.
W. B. Barton, M.D.
J. Chertkow, M.D.
J. Coles, M.D.
G. DeRose, M.D.
L. L. DeVeber, M.D.
A. A. Drieger, M.D.
J. Duff, M.D.
C. A. Dyson, M.D.
R. Finley, M.D.
K. Gay, M.D.
D. Girvan, M.D.
R. E. Greenway, M.D.
J. Harris, D.D.S.
H. Heeneman, M.D.

D. A. MacKenzie, M.D.
R. M. McFarlane, M.D.
T. D. McLarty, M.D.
I. D. F. Schofield, D.D.S.
R. Shearer, M.D.
M. Smout, M.D.
W. K. Stavraky, M.D.
J. Wyatt, M.D.

OCF Ottawa Clinic:

R. P. Abele, M.D.
D. J. Addison, M.B., Ch.B.
G. Armstrong, M.D.
E. A. Atack, M.D.
J. W. Atkinson, M.D.
G. G. Barber, M.D.
M. G. Bard, M.D.
R. Barr, M.B., Ch.B.
P. T. Barron, M.B., Ch.B.
A. W. Barry, M.D.
P. Beaudry, M.D.
R. Belanger, M.D.
D. N. Bell, M.D.
M. Bell, M.D.
M. E. A. Bell, M.D.
C. Benedict, M.D.
B. Benoit, M.D.
P. Benoit, M.D.
J. M. Beresford, M.B., Ch.B.
J. Bormanis, M.D.
A. G. Bouchard, M.D.
M. E. Bourke, M.D.
R. Boutin, M.D.
M. Brazeau, M.D.
B. Burns, M.D.
L. Busque, M.D.
P. Capello, M.D.
C. C. Carruthers, M.D.
C. B. Cattran, M.D.
C. Chadwick, M.D.
C. K. Chew, M.D.
G. C. Cimone, D.M.D.
J. C. Clark, M.D.
J. Collins, M.D.
G. G. Copestake, L.R.C.P. (U.K.)
J. M. Cowan, M.B., Ch.B.
A. Crepeau, M.D.
H. Curry, M.D.
I. Dardick, M.D.
Y. de la Bastide, L.R.C.P. (U.K.)
G. de la Salle, M.D.
J. J. Deneault, M.D.
J. P. Des Groseilliers, M.D.
J. E. Devitt, M.D.
C. Don, M.B., B.S.
J. Drouin, M.D.
P. Drouin, M.D.
F. A. Duggan, M.D.
R. H. Elder, M.D.
C. Ellis, M.D.
R. Elliott, M.D.
R. H. Ferguson, M.D.
R. J. Fairfull-Smith, M.B., Ch.B.
J. F. Fielding, M.D.
J. B. Freeman, M.D.
S. J. Fremeth, D.D.S.
N. G. Futter, M.D.
E. Gear, M.D.
J. Gerin-Lajoie, M.D.
A. Giachino, M.D.
R. R. Gillies, M.D.
Z. Grahovac, M.D.
J. E. Green, M.D.
D. Grimes, M.D.
A. Guberman, M.D.
J. J. Hadju, D.D.S.
P. Hamilton, M.D.
A. Haq, M.D.
J. Hardie, B.D.S.
I. Hart, M.B., Ch.B.
J. Henderson, M.B., Ch.B.
R. Heringer, M.D.
A. Heron, M.D.
C. Hetenyi, M.D.
D. P. Hill, M.D.
R. B. Hladkowicz, M.D.

D. Hooper, M.D.
E. Hsu, M.D.
L. B. Huebsch, M.D.
H. Hugenholtz, M.D.
G. Hurteau, M.D.
J. B. Hurtig, M.D.
A. H. Irvine, M.D.
R. Jackson, M.D.
T. G. Jones, M.B., B.S.
N. Kanigsberg, M.D.
S. P. Kucey, D.D.S.
K. Kuwayti, M.D.
B. Lach, M.D.
G. Laframboise, M.D.
J. E. Laws, M.D.
C. Leahy, M.D.
B. M. Lefebvre, M.D.
B. Leonard, M.D.
E. Liepa, M.D.
J. B. Lightford, D.D.S.
L. Lu-Godbout, M.D.
B. Luke, M.D.
D. D. Macfie, M.B., Ch.B.
P. C. MacEwen, M.D.
J. P. MacLeod, M.D.
N. Mayer, M.D.
W. T. E. McCaughey, M.B., Ch.B.
R. W. McIntyre, M.B., B.S.
W. M. McIntyre, M.D.
D. E. McKay, M.D.
N. V. McPhail, M.D.
S. Meban, M.B., Ch.B.
S. Mercer, M.D.
N. Z. Mikhael, M.D.
D. Moors, M.D.
B. Morton, M.D.
J. E. Mullens, M.D.
R. Nelson, M.D.
P. F. Odell, M.D.
M. Orizaga, M.D.
H. Oxorn, M.D.
R. J. Patterson, M.D.
A. Peloquin, M.D.
E. W. Peterson, M.D.
D. N. Preston, M.D.
P. Rasuli, M.D.
M. T. Richard, M.D.
R. N. Rivington, M.D.
J. Robblee, M.D.
N. A. Russell, M.D.
H. J. Sachs, M.D.
R. Saginur, M.D.
R. Samson, M.D.
G. J. Sarwer-Foner, M.D.
G. Sauve, M.D.
A. C. Scott, M.D.
S. Y. Shirley, M.D.
M. Silverman, M.D.
D. S. Skene, M.D.
R. K. Smiley, M.D.
H. Tao, M.D.
J. R. Taylor, M.D.
E. N. Thompson, M.D.
W. G. Thompson, M.D.
M. Tousignant, M.D.
G. N. W. Tse, M.D.
H. K. Uhthoff, M.D.
F. W. Vaillancourt, M.D.
J. H. Walters, M.D.
H. Warnes, M.D.
A. G. Watson, M.D.
C. Watters, M.D.
D. S. Whittingham, M.D.
K. B. Wilson, M.D.
R. W. Yarnell, M.D.

OCF Toronto-Bayview Clinic:

D. Assaad, M.D.
B. D. Birt, M.B., B.S.
R. H. Comisarow, M.D.
D. H. Cowan, M.D.
G. M. Davies, M.B., B.Ch.
J. L. Freeman, M.D.
L. From, M.D.
J. S. Gruss, M.B., B.Ch.
S. Hanna, M.B., B.Ch.

A. W. Harrison, M.D.
J. Hurwitz, M.D.
J. H. P. Main, D.D.S.
H. A. B. Miller, M.B., B.S.
D. W. Rowed, M.D.
M. L. Schwartz, M.D.
J. S. Senn, M.D.
C. H. Tator, M.D.
G. A. Taylor, M.D.
M. Tile, M.D.
P. M. Webster, M.D.

The Princess Margaret Hospital, Toronto:

P. W. Alberti, M.B., B.S.
U. Ambus, M.D.
A. G. Andrews, D.D.S.
M. A. Baker, M.D.
J. L. M. Bean, M.D.
M. Berry, M.D.
N. Bharatwal, M.D.
M. E. Blackstein, M.D.
T. D. R. Briant, M.D.
A. W. Bruce, M.B., Ch.B.
D. P. Bryce, M.D.
M. B. Buckspan, M.D.
M. L. Bunker, M.D.
G. N. Burrow, M.D.
J. J. Caesar, M.D.
D. H. Carver, M.D.
H. S. L. Chan, M.B.
A. W. Chisholm, M.D.
M. D. Christianson, M.D.
R. H. Comisarow, M.D.
J. G. Connolly, M.D.
J. D. Cooper, M.D.
D. H. Cowan, M.D.
J. S. Crawford, M.D.
L. G. Douglas, M.D.
W. M. Easterbrook, M.D.
R. J. Evans, M.D.
W. K. Evans, M.D.
R. E. Falk, M.D.
E. Farber, M.D.
R. M. Filler, M.D.
E. B. Fish, M.D.
B. K. Fisher, M.D.
J. A. Fisher, M.D.
M. M. Fisher, M.D.
A. E. Franklin, Ph.D.
B. L. Gallie, M.D.
W. O. Geisler, M.D.
A. H. Gerulath, M.D.
R. J. Ginsberg, M.D.
C. M. Godfrey, M.D.
M. Goldberg, M.D.
D. A. Gordon, M.D.
B. J. Green, M.B. Ch.B.
P. Gullane, M.B., B.Ch.
G. Haber, M.D.
J. A. Hakes, M.B., Ch.B.
M. L. Halperin, M.D.
W. J. Hannah, M.D.
L. R. Harnick, M.D.
G. D. Hart, M.D.
D. E. Hastings, M.D.
R. I. Hector, M.D.
C. Hegarty, M.B., B.Ch.
R. C. Hicks, M.B., B.S.
M. E. Hill, M.D.
M. S. Hill, L.R.C.P.
C. H. Hollenberg, M.D.
N. S. Hradsky, M.D.
R. C. Hunter, M.D.
M. A. Hutcheon, M.D.
C. G. Jamieson, M.B., B.S.
R. D. T. Jenkin, M.B., B.S.
M. Jewett, M.D.
D. W. Jirsch, M.D.
A. T. Jousse, M.D.
A. S. Katz, M.D.
A. Keresteci, M.D.
W. K. Kerr, M.D.
M. H. King, M.D.
G. H. Knutson, M.D.
B. Langer, M.D.

F. Langer, M.D.
E. L. Lansdown, M.D.
V. G. Lawson, M.D.
W. D. Leers, M.D.
G. M. Lickrish, M.B., Ch.B.
F. H. Lowy, M.D.
W. J. C. MacArthur, M.D.
R. D. MacDonald, M.D.
I. M. MacKay, M.D.
T. A. MacKenzie, M.D.
I. Macnab, M.B., Ch.B.
L. J. Mahoney, M.D.
J. H. P. Main, D.D.S.
N. E. Marcon, M.D.
W. G. Maxymiw, D.D.S.
P. H. McCleary, M.D.
J. S. McGrail, M.D.
J. W. Meakin, M.D.
T. J. Molony, L.R.C.P. (U.K.)
T. P. Morley, B.M., B.Ch.
C. B. Mortimer, M.D.
P. J. Muller, M.D.
T. M. Murray, M.D.
R. E. Myers, M.D.
J. R. Nethercott, M.D.
R. J. Osborne, M.D.
D. Osoba, M.D.
J. A. Palmer, M.D.
F. R. Papsin, M.D.
F. G. Pearson, M.D.
R. G. Perrin, M.D.
K. Pritchard, M.D.
P. Ramachandran, M.D.
C. A. Ramsay, M.D
J. T. Rankin, B.M., B.Ch.
I. B. Rosen, M.D.
L. Rotstein, M.D.
R. K. Schachter, M.D.
J. Schatzker, M.D.
A. A. Scott, M.D.
M. Scott, M.D.
J. S. Senn, M.D
M. Silberfeld, M.D.
E. R. Simpson, M.D.
G. Foster Smith, M.D.
H. S. Smyth, M.D.
H. A. Smythe, M.D.
M. J. Sonley, M.D.
M. L. Soots, M.D.
A. H. Squires, M.D.
M. Stancer, D.D.S.
R. M. Stone, M.D.
D. J. Sutherland, M.D.
J. M. Symington, B.D.S.
S. A. P. Tindal, M.B., Ch.B.
J. Trachtenberg, M.D.
M. L. S. Vachon, Ph.D.
C. P. Vernon, M.D.
R. Volpe, M.D.
C. P. N. Watson, M.D.
N. A. Watters, M.D.
G. D. Webb, M.D.
R. H. Wilkinson, M.D.
C. C. Williams, M.D.
D. R. Wilson, M.D.
F. R. H. Wrigley, M.B., B.S.
A. Zipursky, M.D.
R. M. Zuker, M.D.

SPECIAL SERVICES

PROVISION OF SPECIAL DRUGS TO TREAT MALIGNANT DISEASE

The Foundation provides special chemotherapeutic agents to cancer patients who are residents of Ontario and are at home under the care of their doctors. This program was undertaken to assist those patients who find the cost of prolonged therapy with expensive drugs beyond their financial resources. In 1982, the drug service provided medications for 1701 patients.

As the number of Ontario residents covered by prescription drug insurance plans (including the Ontario Drug Benefit Plan) continues to rise, the number of patients served by the Foundation's drug service has been decreasing, although in 1981 the number of prescriptions increased by 4%.

TABLE I

Patients Served and Prescription Volume 1973-1982

Year	Patients			Prescriptions
	New*	Old**	Total	
1973	1,827	1,645	3,472	16,484
1974	1,974	1,909	3,883	17,119
1975	1,868	1,811	3,679	16,771
1976	1,722	1,499	3,221	14,702
1977	1,225	1,147	2,372	12,501
1978	1,113	1,108	2,221	12,183
1979	846	911	1,757	10,312
1980	775	860	1,635	9,398
1981	771	801	1,572	9,803
1982	769	932	1,701	9,252

*A "new" patient is one who has received drugs for the first time ever.

**An "old" patient is one who previously was registered in the drug service.

The total cost of the drug service in 1982 was $375,971.20 – an increase of 22% from the $307,676.97 in the previous year (Table II). The cost per patient has increased to $221.03 in 1982 from $195.72 in 1981. The cost per prescription has increased to $40.64 in 1982 from $31.36 in 1981.

TABLE II

Cost of Drug Service
1973-1982

Year	Payments for Drugs	Total Cost of Drug Service
1973	182,210.56	185,756.15
1974	206,189.41	208,541.66
1975	214,942.30	216,055.35
1976	175,949.99	177,984.37
1977	148,418.40	152,021.06
1978	209,817.12	210,836.18
1979	257,136.92	261,512.36
1980	259,973.32	265,059.36
1981	307,376.30	307,676.97
1982	370,388.28	375,971.20

In order of frequency, the principal sites (Table III) treated through the Foundation's drug service in 1982 were: breast – 40%; leukemia – 11%; and Hodgkin's disease – 4%. The increasing use of many new costly therapeutic agents, particularly in the treatment of breast cancer, has contributed to the increasing cost of the drug service.

TABLE III

Number of Patients Served by Major Site of Cancer
1973-1982

Year	Breast	Leukemia	Prostate	Hodgkin's Disease	Ovary	Body of Uterus	Other	Total Patients
1973	763	658	649	160	125	70	1,047	3,472
1974	667	457	753	162	161	51	1,632	3,883
1975	664	491	571	146	189	85	1,533	3,679
1976	863	423	264	128	196	56	1,291	3,221
1977	712	335	72	91	140	41	981	2,372
1978	741	300	51	92	144	46	847	2,221
1979	598	256	42	72	93	47	649	1,757
1980	656	225	23	49	64	35	583	1,635
1981	667	185	20	49	48	26	577	1,572
1982	684	183	21	63	55	20	675	1,701

CARCINOEMBRYONIC ANTIGEN (CEA) AND STEROID-RECEPTOR ASSAYS PROGRAM

The Ontario Cancer Treatment and Research Foundation is administering and monitoring a program for carcinoembryonic antigen (CEA) and steroid-receptor assays which is funded by the Ministry of Health. The CEA assays for *confirmed* cases of cancer and the steroid-receptor assays for *confirmed* cases of breast carcinoma are available, at no charge, to a patient when these assays are performed in the designated laboratories listed below.

During the fiscal period April 1, 1982 to March 31, 1983, 3912 steroid-receptor assays and 29,565 CEA assays have been performed in the designated laboratories.

All laboratories in Ontario are familiar with the program and can provide the details of the data required, sample requirements and specimen transportation. Specimens can be referred to the participating laboratories listed below either directly or through the laboratory which usually provides such services.

Laboratories in the CEA-Assay Program

McMaster University Medical Centre — Dr. E. D. Ryan
1200 Main Street West
Hamilton, Ontario L8S 4J9 tel: (416) 525-9140

Kingston General Hospital — Dr. A. F. Clark
Stuart Street
Kingston, Ontario L7L 2V7 tel: (613) 547-2121

Victoria Hospital — Dr. E. R. Tustanoff
375 South Street
London, Ontario N6A 4G5 tel: (519) 432-5241

Ottawa Civic Hospital — Dr. C. Lapkoff
1053 Carling Avenue
Ottawa, Ontario K1Y 4E9 tel: (613) 729-2511

General Hospital of Port Arthur — Dr. F. J. Lone
460 North Court Street
Thunder Bay, Ontario P7A 4X6 tel: (807) 344-6621

Sunnybrook Medical Centre — Dr. A. Malkin
2075 Bayview Avenue
Toronto, Ontario M4N 3M5 tel: (416) 486-3626

Laboratories in the Steroid-Receptor-Assay Program

McMaster University Medical Centre
1200 Main Street W.
Hamilton, Ontario L8S 4J9 tel: (416) 525-9140
Dr. E. D. Ryan

Victoria Hospital
375 South Street
London, Ontario N6A 4G5 tel: (519) 432-5241
Dr. E. R. Tustanoff

Ottawa Civic Hospital
1053 Carling Avenue
Ottawa, Ontario K1Y 4E9 tel: (613) 729-2511
Dr. T. Ooi

Sunnybrook Medical Centre
2075 Bayview Avenue
Toronto, Ontario M4N 3M5 tel: (416) 487-2722
Dr. D. J. A. Sutherland

University of Toronto
Medical Sciences Bldg., Rm. 7336
Toronto, Ontario M5S 1A8 tel: (416) 978-3553
Dr. G. E. Mobbs

DIAGNOSTIC BIOPSY SERVICE AND VOLUNTARY REPORTING BY PATHOLOGISTS

The diagnostic biopsy service was established by the Foundation to pay for biopsies on uninsured patients. In 1982, 5089 specimens were submitted by dentists (3690 in 1981). Forty-six of these biopsies were malignant.

The number of reports voluntarily submitted by the directors of pathology departments has continued to increase and, in 1982, 41,000 reports were submitted, a 5% increase over the 39,000 reports submitted in 1981.

These reports are used in the generation of cancer incidence data for Ontario and are most valuable in confirming the diagnosis of new cases. The Cancer Act, R.S.O. 1980, Chapter 57, Section 4, Item 7, provides protection for physicians, dentists and hospitals reporting information on cancer incidence to the Foundation. The information from the reports is used for epidemiological and statistical purposes only.

The Foundation gratefully acknowledges the continuing co-operation of the participating pathologists and hospitals, and the support of the Ontario Association of Pathologists in the acquisition of these data.

LODGES FOR AMBULATORY CANCER PATIENTS

At present, the Foundation administers and provides the operating costs for the six lodges for ambulatory cancer patients being seen for diagnosis or treatment at one of the regional treatment centres. Operating from facilities provided by the host hospitals or from free-standing buildings (built from funds raised by the Canadian Cancer Society, Ontario Division, from the people of Ontario and subsequently deeded to the Foundation by the Society), these lodges provide comfortable, supportive accommodation, with minimal supervision, to out-of-town cancer patients under investigation or undergoing treatment at the regional centre.

The cost of this accommodation is borne by the Foundation because regionalization of treatment requires that patients often must travel a considerable distance to the treatment centres (without these facilities, the patients would have required hospitalization at far greater expense to the Province). When beds are available in the hostels, escorts also are accommodated, at minimal cost.

The current facilities, including number of beds and patient days spent in each during the fiscal year ended March 31, 1983, are as follows:

		Number of Beds	Patient Days
KINGSTON	Quinte-Thousand Islands Lodge	26	4,169
LONDON	Thameswood Lodge	50	7,266
OTTAWA	Maurice J. Grimes Lodge	36	6,644
THUNDER BAY	Amethyst House Lodge	18	2,930
TORONTO	Princess Margaret Hospital Lodge	105	23,382

In 1984, we expect to commence construction of a new lodge on the grounds of the Henderson General Hospital in Hamilton to serve the Hamilton Clinic. The Thameswood Lodge, which serves our London Clinic, has expanded in 1983 from 30 beds to 50 beds. Patients who required hostel accommodation while being treated at the Toronto-Bayview Clinic are housed in facilities offered, on a temporary arrangement, by Sunnybrook Medical Centre, or, on occasion, in the Princess Margaret Hospital Lodge. Hostel facilities at Sunnybrook Medical Centre provided the equivalent of 325 patient days in this fiscal year.

TRANSPORTATION OF CANCER PATIENTS

The Foundation covers the cost of transportation of those patients directed to one of its treatment centres or to the Princess Margaret Hospital, who live beyond a 25-mile radius of the centre and are considered in financial need. Usually this transportation is arranged by the local unit of the Canadian Cancer Society, which subsequently is reimbursed by the Foundation.

For the fiscal year ended March 31, 1983, the total cost for transportation of patients was $349,793, compared to $323,405 for the fiscal year ended March 31, 1982.

SPERM BANKING

Infertility following cancer treatment is becoming more common as treatment of malignancy of men in their reproductive years improves survival. Radiotherapy and chemotherapy temporarily or permanently impair spermatogenesis in many cases. A number of pelvic and retroperitoneal surgical procedures can impair erection and/or ejaculation.

For patients who have good semen quality before treatment, sperm banking may be useful. Unfortunately pretreatment semen quality may be deficient particularly with testicular tumors. Hodgkin's disease and non-Hodgkin's lymphoma also may depress sperm counts but patients with most solid tumors have a normal distribution of sperm counts. If the count is less than 40 x 10^6 per mL with motility of less than 40%, the process of freezing frequently produces a high rate of cell death. Whereas we used to exclude these patients from banking, we now still freeze in the hope that in vitro fertilization techniques may allow success even with very few surviving sperm. If this however also fails, unrelated donor semen may be used for subsequent artificial insemination.

Once in liquid nitrogen, semen may be stored for long periods. Insemination has been successful using thawed semen that was stored for more than 10 years. There is no evidence that sperm banking induces significant genetic damage.

At present there are no commercial sperm banks in Canada. A sperm bank for cancer patients at the Wellesley Hospital in Toronto (416-966-6910) is funded by the Ontario Cancer Treatment and Research Foundation. Arrangements can be made directly or through Dr. Michael Jewett (416-966-7804). A fresh ejaculate must be analyzed and assessed for its ability to freeze and thaw. Then a minimum of 3-4 ejaculates are collected with a minimum of two days abstinence between specimens. This collection can be co-ordinated with the work-up of the patient and need not postpone therapy. Facilities at each Foundation clinic are being organized to freeze cells for subsequent transportation to Toronto for storage.

Before patients begin treatment, physicians and surgeons who participate in cancer therapy should counsel patients about potential sterilization. Sperm banking is an option if the patient wishes. No charge is made to cancer patients for this service.

THE NATIONAL BREAST SCREENING STUDY

A. B. MILLER, M.B., Ch.B.*, *Toronto, Ontario*

The National Breast Screening Study (NBSS) began in January 1980 with two primary objectives: to assess screening of the breasts in women age 40-49 with the combination of mammography and physical examination, and to assess the additional benefit, if any, provided by mammography over annual screening by physical examination of the breasts in women age 50-59. These two objectives were designed to answer the most important questions remaining following the pioneering Health Insurance Plan study [illegible] New York. This study, conducted in the 1960s, had demonstrated that screening by mammography and physical examination of the breasts reduced mortality from breast cancer in women over the age of 50 but not in younger women. With the technical improvement in mammography since then it had become critical to determine whether screening younger women would now reduce mortality. It was also desirable to determine whether it was necessary to perform mammography as part of routine examination of the breasts in women over the age of 50. The logistics of setting up screening centres for annual mammography of the total population, even if restricted to women over the age of 50, were daunting and it was essential to justify this.

At the time the study was initiated it was recognized that it would take several years before results on mortality from breast cancer would be available. Therefore, this article will serve to update interested readers on the progress of the study.

Recruitment

The first screening centre opened in Mount Sinai Hospital in Toronto in January 1980. At the time of writing (November 1983) recruitment continues into this centre with over 13,500 women accrued. The second centre opened in Quebec City in August 1980 with a target of 6000. This target was exceeded within two years and over 8000 women have now been recruited in Quebec City. Three centres were opened in the early summer of 1981: in Montreal at the Institut du Cancer; Hamilton at the Henderson General Hospital; and Winnipeg at the Manitoba Cancer Treatment and Research Foundation. The initial target in Montreal was 6000, but this was changed to 9000 within six months. This centre now has almost completed its recruitment. The target in Winnipeg was 9000. They have now reached this target and have agreed to continue recruiting with an aim of 10,000. The target in Hamilton was 4500, but due to unexpected difficulties it was necessary to cease formal recruitment at just below 4000. Rescreening, however, continues in that centre.

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*Director, Epidemiology Unit, National Cancer Institute of Canada, Toronto.

New centres have been opened during the current year in Ottawa, with a target of 6000, and in London, with a target of 4500, in association with the clinics of the Foundation. New centres also opened in Halifax (6000), a second centre in Montreal at the Hotel Dieu Hospital (4500), and in Vancouver (11,000). We have now recruited over 51,000, i.e. past the halfway point for our target of 90,000. We are opening two centres in Alberta — in Edmonton and Calgary, with a combined target of 9000, but because of delay in securing support for these centres they will not start screening until January 1984. Other centres also are considering participation in the study. We plan to terminate all accrual into the study on March 31, 1985.

In some centres — particularly Quebec City, Montreal and Winnipeg, recruitment has been steady. Quebec City recruitment largely followed from use of local networks — bulletins in parish newsletters for example, radio and television, and word of mouth. In Montreal recruitment has required regulary two monthly bursts of publicity in newspapers, radio and television. It was facilitated by the appointment of a local television personality as local patron — a woman who offered herself for screening and has continued to support the study actively. In Winnipeg recruitment has followed a number of publicity mechanisms facilitated by active involvement of Canadian Cancer Society district and unit offices; as a result, a fairly high proportion of women from surrounding communities have entered the study. The most dramatic example of this participation was a group of women who chartered a school bus and drove from Sioux Lookout, Ontario to Winnipeg, starting out at 2:00 a.m. in the depth of winter and returning to their homes approximately 24 hours later.

In Toronto, however, recruitment has been slow — in part because of concern over the presumed hazards of mammography. The radiation dosage used in mammography in the NBSS is extremely low; about 0.2 rads per mammogram. A number of studies support the assertion that this level of radiation is likely to have a very negligible effect on the age group of women participating.

Last year recruitment everywhere had a substantial boost from a Health and Welfare Canada insert describing the study distributed with family allowance cheques throughout the country. This generated more than 2500 appointments.

In order to benefit from their endorsation the Board of Patrons was appointed. The Board includes the Federal Minister of Health, Monique Bégin, herself a participant in the study in Montreal; the former Lieutenant-Governor of Ontario, Pauline McGibbon; the wife of our Premier, Mrs. Wm. Davis; and prominent personalities from many walks of life including June Callwood, Principal Joan Foley, Celia Franca, Christina McCall Newman and Joan Sutton of Toronto. The Board also includes Suzanne Lapointe of Montreal, Lucie Pépin of Ottawa and the Honorable Pearl McGonigal of Winnipeg.

After the establishment of the Board of Patrons, we began to recruit by writing letters to women identified through appropriate listings in the Toronto area with follow-up phone calls. We are now recruiting at the rate of 200-300 a month in Toronto through these letters.

Follow-Up

In a study based on four rescreening examinations it is important that a high proportion of women return for their re-examinations and that we maintain contact with all, whether or not they return. So far it would seem that about 80% of the women re-attend for their second and third year screening.

The follow-up process is achieved by a letter, generated by our Unit computer, sent a little over a month before the woman's anniversary of her first attendance. These letters, which go out on a screening centre's letterhead, elicit a 60% spontaneous response for appointments. For the rest we depend on part-time staff who telephone, often in the evening, and make the appointment. We estimate that our follow-up costs per individual are of the order of $1.15.

Even for those who do not re-attend the screening centre the majority provide some information. Special endeavours are made to trace those who do not respond, and currently we are in touch with 95% of the women who have entered the study.

Breast Self-Examination

All women in the study are taught breast self-examination (BSE). This has provided an opportunity to assess approaches to teaching, the evaluation of the extent to which women carry out BSE after being individually taught, and eventually this may enable us to attempt some indirect assessment of its value. The method used in the screening centres is the radial method, as distinct from the circumferential method taught by the Canadian Cancer Society. We chose the radial method because we believe it is slightly better at covering the totality of the breast.

We are finding that almost one-half of the women are doing BSE 12 times a year — a frequency that is much better than in the general population. Over time we hope to improve the quality of their performance. A number of woman have attributed the early detection of cancers between screening examinations to their practice of breast self-examination. Indeed, several of them regard this as a positive benefit of the study.

Physical Examination of the Breasts

In all centres, except the Province of Quebec, physical examination of the breasts is done by trained nurse-examiners. Nurses are trained by the study surgeons in each centre. After an initial training period, varying from two weeks to a month, the nurses commence examining women in the centre. Initially we find a high proportion of the women they examine is referred to the study surgeon for assessment. The study surgeon makes the recommendations to the family physician. After a relatively short period the nurse-examiners acquire examining skills equal, if not superior, to most physicians. Approximately 15% of the cancers identified in the screening centres are found on physical examination alone, being invisible on mammography even when one knows where to look. Such cancers are often small and infiltrating, a few with one or two nodes already involved, different from the cancers found on mammography alone. Nevertheless, they appear to be biologically early and it is conceivable that much of the initial benefit from screening will be derived from the early detection of what might otherwise become rapidly progressive advanced disease.

In the Province of Quebec, because of provincial regulations, part-time physicians are used.

Mammography

In all centres, low dose, screen-film techniques are used, because the radiation dosage used in film screen mammography is about 1/5 of that required for xerography. All mammography machines and image quality are regularly monitored by our reference physicist, Dr. M. Yaffe of the Radiological Research Laboratory, University of Toronto. Dr. Douglas McFarlane of Toronto Western Hospital acts as the reference radiologist for the study. Samples of films from each of the centres are reviewed by Dr. McFarlane. As a result, we have been able to estimate the extent to which there is variation in approaches to diagnosis throughout the study.

Recommendations for Treatment

A screening centre only can make recommendations to the woman and to her usual medical advisor with respect to the management of any abnormality discovered. If it is obvious that a cancer has been detected, the surgeon calls the woman's family physician to alert him to the diagnosis. Most of the abnormalities will be benign but of the abnormalities discovered on physical examination which require biopsy, about 1 in 4 will be cancer compared to about 1 in 10 of those found on mammography alone. On physical examination and on mammography, the signs of early cancer often are indistinguishable from benign disease until a diagnostic biopsy has been performed. It is up to the woman's family physician to decide where she will be treated. In most centres a high proportion are referred back to the study surgeon for management — a higher proportion of those found on mammography alone than of those with clinically palpable abnormalities.

Management of the lesions therefore varies and cannot be regulated in the study. Management even varies between the study centres. Thus, for example, most of the women with abnormalities identified on mammography alone in Toronto have needle localization biopsy under radiologic control. In Quebec, on the other hand, most such abnormalities initially would have needle aspiration cytology. In all centres it is clear that a higher proportion of early cancers have been diagnosed than would be expected in routine practice and this has meant that a higher proportion of women with cancer has been treated with more limited surgical procedures — a benefit of screening.

Currently the cancer detection rate on initial examination approximates to 3 per 1000 in women age 40-49 and 6 per 1000 in women age 50-59 and a little less than one-half of these rates on rescreening. The numbers of interval cancers are low but are higher in younger than older women.

Risk Factors For Breast Cancer

The study provides the opportunity to increase our knowledge of the epidemiology of breast and other cancers. In order to facilitate this, and in the light of our interest in the association of diet and cancer, within the last year all study participants have been asked to complete a self-administered dietary questionnaire. A high proportion of women is completing these and returning them so that we will be able to add dietary information to the information on risk factors for breast and other cancers which are collected when women enter the study.

In summary, the National Breast Screening Study is on course with a demonstrated ability to recruit women into screening centres and with the success of the study procedures now well documented. Screening is scheduled to end in all centres in 1988 and it is possible that shortly following that we will have preliminary results. However, if the benefit in younger women from screening is low, possibly for biological reasons, and if the contribution of mammography in older women is not as great as some have claimed, it may well be some time before we will be in a position to report definitive findings. If that proves to be so, however, it will have shown the wisdom of not rushing into the introduction of mass screening for breast cancer in Canada.

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RESEARCH PROGRAMS

SUMMARY OF OCTRF RESEARCH

As reported last year, the Foundation is in the process of phasing out the grants-in-aid program in order to provide additional funding for the support of career scientists in the Foundation clinics and health sciences centres throughout the province. As funds become available, the Foundation proposes to support up to 20 career scientists (4 per university-affiliated clinic) and 10 research associates or scholars in the health sciences centres.

Grants-in-Aid Program

Although the Foundation did not hold a competition in 1982, nine projects, which were approved in the 1981 competition as "two-year term grants", are being funded for the period April 1, 1983 to March 31, 1984, in a total amount of $334,189. In addition to this, it is anticipated that grantees will spend approximately $300,000 during the current year as they continue research already approved. However, the Foundation has advised grantees that by April 30, 1984 they must return any funds remaining from awards made up to and including April 1, 1982, and that residual fund from awards made up to April 1, 1983 must be returned by April 30, 1985, thereby permitting a final phasing-out of the grants-in-aid program. As they become available, the funds accruing from this process will be used to recruit additional research scientists.

We are conscious of the problems grantees face in obtaining peer-reviewed grant support, and remain hopeful that, at some time in the future, the Foundation will provide some support for this purpose. A request has been made to the Ministry for additional funds to initiate a modified grants-in-aid program, focussed on provincial priorities.

Support for Research Personnel

Generally funds for the support of research personnel are derived from the Foundation's research funds comprised of the annual legislative vote provided by the Ministry of Health, and from donations and bequests. During the current year, however, the Foundation has appointed two career scientists, who will receive salary support plus "start-up" funds from the Terry Fox Research Fund (Ontario). This fund was established in 1980 as a result of an award of $1,000,000 from the Provincial Government for the support of young career scientists working in cancer research. However, in accordance with an agreement with the Ministry, only the interest on this amount is available to the Foundation for the first five years, after which the Ministry and the Foundation will reassess the disbursement policy.

In accordance with recommendations made by an ad hoc committee and subsequently approved by the Board, a Subcommittee on Support of Research Personnel was established in 1983, under the chairmanship of Dr. D. M. Robertson, Professor and Head of the Department of Pathology at Queen's University, and for many years a member of the Research Committee. This committee, which includes representatives from the scientific and geographic areas through the province, is charged with the appointment (and reappointment) of career scientists to the Foundation clinics and research scholars to the health sciences centres. Generally, no changes have been made in the terms of reference for career scientists already employed in the clinics, except that now the mechanism for the appointment of these individuals is streamlined. Recommendations for these awards are made jointly to the Executive Director of the Foundation by the Clinic Directors and the Dean of the affiliated faculty of medicine. A local selection committee, which includes the clinic director, other scientists and representatives from the university, interviews the candidates and submits its recommendations to the Subcommittee on Support of Research Personnel. The latter committee then considers both the qualifications of the individual(s) and the list of equipment, etc., required to initiate the individual's research program. The candidate is expected to spend at least 75% of his time on research, but may participate in clinical service or teaching on a limited basis. The Foundation provides a salary, appropriate research space and minimal core support; the candidate is expected to obtain operating funds through other granting agencies. The career scientist, who must have a cross appointment in the affiliated university, may consider his a "life-time" appointment, but must maintain peer-reviewed grant support, publish in peer-reviewed journals and pass periodic site reviews, as deemed necessary by the subcommittee. Once approved by the Board, these appointments may commence at any time during the year.

In contrast to the mechanisms involved in the appointment of career scientists, the Dean of Medicine in the health sciences centres selects candidates to compete in research scholarship competitions held by the Foundation. The competitions will be held annually or periodically as funding permits. The terms of reference for research scholars are similar to those of career scientists, except that the appointments are limited to a five-year term, once renewable. The host institution provides the research facilities and core support. Currently, the Foundation supports seven research associates in the health sciences centres; these appointments were made on the basis of "life-time" appointments subject to the same criteria as a career scientist. The support of these individuals will continue in accordance with the terms of the original appointment.

During 1983/84, the Foundation continued the support of three career scientists — two in the Kingston Clinic and one in the London Clinic. In addition, two career scientists were appointed to the London Clinic effective April 1 and November 1, 1983, respectively and are being supported through the Terry Fox Research Fund (Ontario). As noted above, the Foundation provides salary support for seven research associates in the health sciences centres. The Foundation also provides salary support for the senior scientific staff at the Ontario Cancer Institute — approximately 28.5 full-time equivalents. The total costs of such support during 1983/84 is approximately $1,708,655.

In accordance with our agreement with the Ministry, scientists supported through the Terry Fox Research Fund (Ontario) will receive an annual salary, plus start-up funds for essential equipment, etc. To date, approximately $157,608 has been committed from this source for 1983/84. However, recognizing that the annual interest available from this fund (based on current rates) will not provide support for any additional career scientists, we anticipate that the balance (funds which have accumulated since September 1980) will be used during the current year to purchase equipment, etc., to establish at least one career scientist in the Ottawa Clinic, and an additional career scientist at the London Clinic. Recommendations for these appointments have not been finalized.

In addition to these appointments, the Foundation hopes that at least four more career scientists will be appointed in the near future — two in the Hamilton Clinic, one in the Kingston Clinic, and one in the Ottawa Clinic. When appropriate research space is available at the Toronto-Bayview Clinic, the Foundation plans to establish a research unit there, similar to that in the other Foundation clinics.

Research Scholarship Competition

The Foundation held a research scholarship competition in October 1983 and received six applications (two from each centre — Hamilton, London, and Toronto). These applications have been reviewed by the Subcommittee and its recommendations will be submitted to the Research Committee and the Board early in 1984. Depending upon available funds, at least one research scholar, and possibly two, will be appointed for support commencing July 1, 1984. In addition to providing salary support, the Foundation will provide $5000 (if required) for start-up funds.

Core Support

In addition to providing salary for career scientists working in the clinics, the Foundation provides minimal core support for common needs such as secretaries, glasswashing, etc. A total of $81,956 was awarded to the Kingston and London Clinics for this purpose in the current year. The Foundation also provides similar support for the senior scientific staff at the Ontario Cancer Institute — an amount of aproximately $550,000 for 1983/84.

Mary Parkes
Research Secretary

The Ontario Clinical Oncology Group

In the summer of 1982, the Research Advisory Committee of the Foundation established an Ontario-wide, clinical-trials group. Dr. P. B. McCulloch, Head of Medical Oncology at the Hamilton Clinic, was named co-ordinator and the Department of Biostatistics at McMaster University Medical School agreed to act as biometry centre and consultant in methodology.

Initial funding has been obtained through a grant from the Ontario Provincial Lottery.

The Foundation is in an exceptional position to initiate and carry clinical trials to a successful conclusion, because of the quality of the scientific and clinical staffs affiliated with it, its access to computerized patient records and a wealth of patient material available through the Foundation clinics and the Ontario Cancer Institute — 16,000 new cases in 1978. Accordingly, a Policy Committee was established with representation from each regional centre, the Ontario Cancer Institute, and the provincial medical schools and a meeting convened in the fall of 1982. Subsequently, over 250 individual investigators were circulated with invitations to submit brief proposals for clinical trials. Over the winter of 1982/83, roughly 10% of these people did submit proposals. All proposals are peer-reviewed and, from the initial 15 submissions, one trial was chosen for expansion, feasibility analysis from a statistical point of view, and ultimately for activation in the fall of 1983.

This first trial, which was proposed by Drs. R. Clark, H. Bush, L. J. Mahoney and R. H. Wilkinson, will involve women with small primary breast cancers deemed surgically disease-free after limited resection of the tumor and a small amount of remaining breast tissue: axillary-node dissection showing no pathologic involvement. After informed consent, such patients will be randomized to receive, after operation, local radiation to the affected breast or observation alone. This trial should answer the important questions concerning the effects of such adjuvant radiotherapy on local and distant recurrence, and on long-term survival. The radiation oncologists are enthusiastic, and the Ontario Cancer Institute and the regional clinics have agreed to participate. Enthusiasm for this study is also rising among surgeons throughout the province, who refer patients with breast cancer.

A second group of proposals has been peer-reviewed but no decision has been made concerning activation of a second co-operative clinical trial. Close co-operation is being maintained with the National Cancer Institute of Canada Clinical Trials Group by continuous consultation. This avoids duplication of effort and allows us to perform trials, which can be run efficiently within a populous but geographically small area, without deterring our investigators from participating in trials which require a national base.

The Ontario group is off to a good start and should be able to demonstrate its scientific merit and cost-effectiveness over the next two to three years.

P. B. McCulloch, M.D., F.R.C.P.(C.)
Program Co-ordinator

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McMaster University, Hamilton

ONCOFETAL ANTIGENS DETECTED BY SERA FROM PREGNANT WOMEN*

P. B. DENT** and S. K. LIAO†, *Hamilton, Ontario*

Our previous studies of sera from patients with malignant melanoma revealed antibodies which react with a variety of human tumors maintained in cell culture. The reactivity is directed against a spectrum of antigens, none of which are melanoma-specific and most of which are not even specific to cancer cells. After detailed absorptions with a variety of normal and non-melanoma neoplastic cells, the sera no longer reacted with melanoma target cells. However, we did observe that those sera, which contained non-specific antibodies, came predominantly from women. Because it is well known that females with melanoma have a better prognosis than males, and that many, if not all, human tumor-associated antigens are oncofetal, we instituted this study of oncofetal antigens defined by sera from postpartum females.

We screened a panel of 32 sera from such women for antibody against melanoma cell lines and found that 12 contained reactivity against one or more of these cell lines. Eleven of the 12 sera showed strong reactivity against normal lymphocytes by complement-dependent lymphocytotoxicity tests, whereas only 1 of the 2 sera, which lacked antibody to melanoma cells, contained lymphocytotoxic antibody. Reactivity with melanoma cell lines did not correlate with any particular histocompatibility antigen specificity. Furthermore, reciprocal absorptions with melanoma cells and lymphocytes permitted differential removal of melanoma and HLA reactivity. Experience with tests of absorption with different melanoma cell lines has made it apparent that the spectrum of antigens present on melanoma is quite broad and complex. We have concluded that the definition of oncofetal antigens using polyclonal human isoantisera is unlikely to be successful, and studies in our laboratory now are limited to those using monoclonal antibodies.

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*Project 276. (Formerly titled "Serology of Human Malignant Melanoma")

**Professor of Pediatrics and Pathology, McMaster University, Hamilton; and Consulting Immunologist, Ontario Cancer Foundation Hamilton Clinic.

†Associate Professor of Pathology and Pediatrics, McMaster University; and Ontario Cancer Foundation Research Associate, Ontario Cancer Foundation Hamilton Clinic.

ABSORPTION AND METABOLISM OF EQUINE ESTROGENS IN NORMAL MEN AND POSTMENOPAUSAL WOMEN*

B. R. BHAVNANI**, C. A. WOOLEVER** and C. C. PAN†,
Hamilton, Ontario

In continuation of our studies dealing with the equine estrogens and their metabolic fate in postmenopausal women, we have investigated the interaction of equine estrogens with human serum proteins.

Conjugated equine estrogen preparations, such as Premarin, contain sulfate esters of the ring-B, unsaturated estrogens — equilin, equilenin, 17α-dihydroequilin, 17α-dihydroequilenin, 17β-dihydroequilin and 17β-dihydroequilenin, and classical estrogens — estrone, 17β-estradiol and 17α-estradiol. The major components are estrone sulfate (45%) and equilin sulfate (25%). They are used extensively as replacement therapy for estrogen-deficient women. Recently, they have been implicated in the genesis of some cases of carcinoma of the endometrium.

In our previous studies[1] we have reported that the metabolic clearance rate (MCR) of equilin sulfate in women and men was 176 ± 44 L/m^2/day, and that this value is only 6-8% of that calculated for the unconjugated equilin (3300 and 1982 L/m^2/day). The low MCR of equilin sulfate, in contrast to that of unconjugated equilin, may be due to its binding with human serum albumin and other blood-binding proteins, such as sex-hormone-binding globulin (SHBG). Furthermore, it is generally believed that only the "free" (dialyzable) steroid hormone in the circulation is biologically active. Thus in the case of estrogens (and androgens), the serum SHBG levels play an important part in the regulation of the amount of free estrogen available for biological action. No information is available regarding the binding of equine estrogens to serum proteins. In the present investigation the binding affinity |Ka(ml/pmol)| of equilin and equilin sulfate with human serum proteins was determined and compared with that of estradiol, estrone, dihydrotestosterone and testosterone.

Sephadex gel filtration was used to determine the nature of binding of equilin, equilin sulfate, estradiol, estrone, testosterone and dihydrotestosterone to serum proteins as follows: undiluted serum (0.4 - 0.6 ml) obtained from postmenopausal women was incubated with approximately 5 pmole/ml of ^{3}H-labelled steroid at 37°C for 30 minutes. The mixture was then cooled to 4°C and subjected to Sephadex G-150 column chromatography. Approximately 100 fractions of 0.7 ml were collected and analyzed for radioactivity and protein. With each of the above steroid hormones, except equilin sulfate, two major peaks of radioactivity were observed and these were associated with proteins with approximate molecular weights of 132,000 (SHBG) and 67,000 (albumin) daltons. (In the case of equilin sulfate, we did not detect binding to SHBG, however, the major radioactive peak was associated with albumin.) Binding to SHBG was confirmed by treating the incubated serum with Con. A-Sepharose 4B Gel (removes glycoproteins such as SHBG) and then subjecting the sample to gel filtration on Sephadex G-150. Under these conditions the radioactive peak associated with SHBG was absent[2].

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*Project 388.

**Professor of Obstetrics and Gynecology, McMaster University, Hamilton.

†Graduate Student, McMaster University.

Comparison of the SHBG Binding Affinity of Various Steroid Hormones

[Ka(ml/pmol)]

Post-menopausal Women	Equilin	Estrone	17β-dihydro equilin	Estradiol	Testos-terone	Dihydro-testos-terone
1	0.10	0.74	0.08	0.36	3.4	1.1
2	0.32	0.20	0.85	—	—	—
3	0.07	0.05	0.09	0.20	0.52	4.1
4	—	—	0.01	0.01	0.26	1.7
5	—	0.33	0.06	0.09	1.85	6.6
Mean	0.16	0.33	0.22	0.17	1.5	3.4
SD	0.13	0.29	0.35	0.15	1.5	2.5

The relative binding affinities [Ka (ml/pmol)] of equilin, 17β-dihydroequilin, estrone to SHBG were determined by the DEAE-filter assay[3], and the data were analyzed by the competitive Scatchard analysis[4]. The results are shown in Table I. These results indicate that both estrogen and androgens bind to SHBG with high affinity. Affinity of T and DHT for SHBG is approximately 10-20 times higher than that observed for estrogens, however, no significant difference is observed between the ring-B, unsaturated equine estrogens and the classical estrogens.

In conclusion, the gel filtration data and the DEAE filter assays indicate that the equine estrogens, such as equilin, bind to serum proteins such as SHBG and albumin, in a manner similar to the classical estrogens — estradiol and esterone. Thus, these and our previous studies clearly indicate that the ring-B, unsaturated equine estrogens express their biological activity by mechanisms similar to those described for the classical estrogens — estradiol and estrone. Therefore our studies do not support the hypothesis that the use of conjugated equine estrogens *per se* rather than the classical estrogens results in increased risk of endometrial cancer[5,6].

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PRESENCE AND REGULATION OF GAP JUNCTIONS IN CANCEROUS AND NONCANCEROUS TISSUES*

R. E. GARFIELD** and D. R. INMAN**, *Hamilton, Ontario*

It is postulated that the growth and proliferation of cells is controlled through gap junctions — specialized cell-to-cell contacts through which direct intercellular communication is believed to occur. The objectives of this ultra-structural research were:

- To determine the relative abundance of gap junctions in normal and cancerous human breast tissues.
- To explore the relationship between the growth of myometrium and the control and regulation of gap junctions in response to steroid hormones.

By thin-section electron microscopy we examined normal and malignant human breast tissue samples and myometrial tissues from immature rats following treatment with steroid hormones.

There were gap junctions and desmosomes (cell-to-cell contats characteristic of epithelial cells) between cells of the mammary ducts in all normal human breast samples examined. In all mammary tumors examined, however, no gap junctions were found although the distribution of desmosomes appeared normal. Gap-junction development in the myometrium was stimulated by estradiol; when progesterone was administered simultaneously, however, it was suppressed. Estradiol induced increased hyperplasia and hypertrophy in the myometrium, which preceded gap-junction development.

Our preliminary conclusions are:

- Gap junctions appear to be absent from human breast cancer cells although they are present in normal breast.
- The resulting lack of direct cell-to-cell communication may be one of the mechanisms underlying uncontrolled tumor growth.
- Growth and gap-junction development in the rat uterus appear to be regulated by steroid hormones.
- The absence of gap junctions appears to be necessary for uterine growth.

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*Project 458.

**Professor of Neurosciences, McMaster University, Hamilton.

Ontario Cancer Foundation Hamilton Clinic

CLINICAL INVESTIGATIONS

Dr. W. M. Hryniuk, Director of the Hamilton Clinic, reports on the following clinical research investigations:

ELECTRON BEAM THERAPY OF MYCOSIS FUNGOIDES

A unique combination of resources allows whole-body electron therapy of mycosis fungoides to proceed under optimum conditions. Dr. A. Tadros directs the project, which attracts patients from the entire country at the rate of three new cases per month. A recent 10-year analysis of results indicates that, while the disease is chronic — when patients die, they die of their disease. We have identified a subgroup of patients, T_2N_0, who enjoy a long disease-free survival. This subgroup may not require additional treatment, may be controllable with electron beam therapy as the sole modality. This possibility allows us to design a trial of electron therapy, plus or minus adjuvant treatment for other subgroups.

ENDORECTAL RADIATION OF RECTAL CARCINOMA (PAPILLON TECHNIQUE)

Dr. V. Basrur co-ordinates a group that is testing the use of endorectal radiation of selected cases of rectal carcinoma. With this technique, a small but well-defined group of patients can be spared abdominoperineal resection and colostomy.

INTENSIVE AND BRIEF CHEMOTHERAPY AFTER MASTECTOMY IN PREMENOPAUSAL STAGE II BREAST CANCER

In co-operation with the London Regional Centre, a multiple drug combination is being tested in patients under the age of 50 with axillary nodal involvement at the time of mastectomy. The results of a four-year pilot study compare favorably with historical controls treated with melphalan or radiotherapy. Encouraged by these results, we have opened a randomized trial comparing 12 weeks with 36 weeks of treatment in co-operation with the London Regional Centre.

PILOT STUDIES IN STAGE IV BREAST CANCER

A multiple drug combination is being given to selected patients with disseminated breast cancer, with the objective of inducing pathologically-restaged complete remissions.

COMPARISON OF TREATMENT POLICIES IN POSTMENOPAUSAL STAGE II BREAST CANCER

The role of adjuvant chemotherapy is uncertain in patients over the age of 50 who have axillary-node involvement at the time of mastectomy. Accordingly, patients in this group, who are referred to the Hamilton Clinic, are randomized to see either a radiation or a medical oncologist for consultation and treatment.

DRUG-SEQUENCE IN CHEMOTHERAPY OF HEAD AND NECK CANCER

Dr. G. Browman is co-ordinating a randomized trial to determine the optimum sequence for the administration of fluorouracil and methotrexate. The trials are designed to test a biochemical model describing the interaction of the two drugs. The first trial demonstrates no advantage for a one-hour delay between the two drugs (contrary to all expectations). An 18-hour delay is now being tested.

IN VITRO STUDIES OF ACUTE MYELOBLASTIC LEUKEMIA (AML) CELLS

Dr. G. Browman is testing the in vitro sensitivity to drugs of AML cells. The same drugs are being used in an intensive chemotherapy regimen aimed at curing AML. The study is being done in collaboration with six American centres and the consortium is supported by NCIC Grant RIO CA 28734-01.

STUDIES IN SMALL-CELL-LUNG CARCINOMA (SCLC)

Dr. A. Figueredo is co-ordinating a series of studies to define the optimum treatment of SCLC. A randomized trial has been completed testing regular-dose versus high-dose chemotherapy under cover of Septra. The prophylactic Septra has allowed the administration of higher doses of drugs but this has not improved remission rates or survival. A new trial has been opened to test in this disease the concept of dose-intensity of multiple drugs.

STUDIES IN OVARIAN CANCER

We have just closed a new pilot study of weekly intensive Adriamycin/cis-platinum therapy of Stages III and IV ovarian cancer. Preliminary analysis suggests that the results are much superior to the usual regimen of cyclophosphamide/Adriamycin/cis-platinum given every four weeks. A study of a variation on this regimen has been opened under the aegis of the NCIC to confirm or refute these results.

CO-OPERATIVE GROUP TRIALS

Selected protocols of the NCIC and NASBP are being followed for myeloma, Hodgkin's disease, non-Hodgkin's lymphoma, non-small-cell carcinoma of the lung, melanoma, ovarian carcinoma and breast cancer.

Queen's University, Kingston

REGULATION OF GRANULOPOIESIS IN LEUKEMIA*

P. R. GALBRAITH**, *Kingston, Ontario*

This study was done to learn more about those control mechanisms, which regulate granulopoiesis, and ultimately to determine how these mechanisms are exploited by clonal hemopathies such as leukemia. The cloning of granulocytic progenitor cells is dependent upon colony stimulating activity (CSA). We have found that sources of CSA such as mononuclear-leukocyte-conditioned medium (MNL-CM) contain at least two types of activity and that these vary independently of one another[1]. Colony amplification factor causes a dose-related linear increase in mean clonal size (MCS) and shortens the time to terminal differentiation and death of a colony. This activity is essential for colony formation. Recruitment factor is not essential for cloning but influences the number of clonogenic cells, which will be affected by amplification factor. The number of colonies (defined as 24+ cells) present in a culture at a given time depends on both factors, and upon clonal death rate.

These findings permitted us to develop a simple in vitro model to analyze control mechanisms. Although it has been proposed that neutrophil products inhibit cloning by reducing CSA production, neither our kinetic data nor published data are compatible with this hypothesis. Neutrophils release diffusible (MW <12,000) and non-diffusible (MW >12,000) moieties, which affects the response to preformed CSA; these factors may have a positive or negative effect on clonal recruitment and/or amplification in agar culture, and on the rate of DNA synthesis by granulocytic precursors maintained in liquid cultures (analyzed by flow cytometry)[2]. These factors appear to act indirectly via a regulatory cell network, whose composition was altered in a series of experiments using monoclonal antibodies (OKT_3, OKT_4, OKT_8, OKM_1, B_1) to deplete (with complement) various subpopulations in human bone marrow[3].

Our data suggest, however, that cellular components of the regulatory network are not marked by the monoclonal antibodies in any consistent fashion. Further studies of these interesting phenomena are warranted before one can approach the more difficult problem of clone — clone interactions in leukemia.

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*Project 309. (Final Report)

**Professor of Medicine, Division of Hematology, Queen's University, Kingston.

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BREAST LYMPHATIC TRANSPORT KINETICS*

E. E. STERNS**, T. CHALLIS†, D. DEXTER‡ and
J. S. LOTT‡, *Kingston, Ontario*

Our studies on the rate of disappearance of isotope-tagged albumin into the breast, adjacent to an area of proven carcinoma, have now been completed. Fifty-two patients have been studied with follow-up ranging from two to six years. The results indicate that disappearance rate of the isotope is different in patients who develop early metastases (less than 24 months) than in those who develop metastases at a later stage or remain disease free. This phenomenon raises questions concerning the underlying pathophysiological derangements, which may relate to microvascular abnormalities in these breasts.

The rate of isotope disappearance in patients with cancer who remain disease free for more than 24 months did not differ from those who had breast lesions which were histologically benign.

We believe that the study suggests a functional disturbance at the microvascular level and that further studies should be done to establish the relevance of this finding and, if confirmed, the underlying mechanisms.

The unfortunate aspect of our study was that the variability in disappearance rates did not allow us to get results which were statistically significant.

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*Project 330.

**Professor of Surgery, Queen's University, Kingston.

†Professor of Diagnostic Radiology, Queen's University.

‡Lecturer in Pathology, Queen's University.

‡Director, Ontario Cancer Foundation Kingston Clinic; and Professor of Radiation Oncology, Queen's University.

HUMAN NATURAL KILLER CELLS — BASIC AND CLINICAL STUDIES*

H. F. PROSS**, *Kingston, Ontario*

The term natural killer (NK) cell refers to a population of lymphocytes in normal individuals, which are characterized by their ability to destroy certain tumor cells. NK cells occur "naturally" and are present in high frequency (1-3%) in the blood of all normal donors and in patients with cancer [1-3]. Natural killer cells are only weakly active against fresh human tumors, although it is now well established that when the tumor cell can be killed by an NK cell, it is more difficult to transplant that tumor and it is less likely to metastasize. Over the last several years we have done both basic and clinical studies into this phenomenon. At the basic level, we have perfected methods for studying human NK cells at the single cell level[4], which have permitted us to estimate the actual number of killer cells in the blood of normal and cancer donors. We have established that the level of NK activity in normal donors is farily consistent for each particular person[5]. Most of this individual activity is attributable to the frequency of NK cells in the blood, as opposed to differences in the activity of the individual killer cells. We have identified patients who have a markedly reduced frequency of NK cells and one patient who had a leukocytosis of his NK cells[6]. This patient was the first recorded case of NK leukocytosis. Over the past year, we have developed a data base program for use on a microcomputer so that all of any relevant clinical data on the patients under study can be recorded and retrieved and that we may compare clinical variables with our experimental results. Our primary aim in these studies is to determine whether there is any correlation between the level of NK activity and the length of time a particular cancer patient remains free of recurrent or metastatic disease. The facility will also allow us to determine the relationship (if any) between chemotherapy, radiotherapy, and immunotherapy and cytotoxic function.

At present we have analyzed two sets of data: (1) the NK activity of patients receiving complete Freund's adjuvant (CFA) plus or minus specific lung antigen in the NCIC Bronchogenic (II) Trial in the conjunction with Dr. J. A. Maroun of the OCF Ottawa Clinic[7]; and (2) the effect of benign breast disease and other risk factors of NK function in patients attending the Kingston Breast Screening Clinic (in conjunction with Dr. E. Sterns of the Department of Surgery)[8]. In the former study we observed that stimulation with CFA augmented NK activity, and that cytotoxicity against a lung-tumor-cell line was also enhanced. This enhancement appeared to be largely due to the non-specific stimulation by CFA as opposed to the lung antigen per se. In the study of patients in the breast screening clinic, we observed that high-risk patients had an augmented level of NK function but that, when the patients were subdivided into the type of risk, the elevation was due entirely to the presence of those with benign breast disease.

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*Project 392. (Final Report)

**Career Scientist, Ontario Cancer Foundation Kingston Clinic; and Professor of Radiation Oncology and Associate Professor of Microbiology and Immunology, Queen's University, Kingston.

In basic studies, we have determined that if a tumor is forced to differentiate into a more mature form, its cells become less sensitive to natural killer cell activity[9]. In addition, certain sugars will interfere with cytotoxicity[10]. This observation may be relevant to events, which occur in vivo.

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PROGNOSTIC AND PREDICTIVE VALUE OF BREAST THERMOGRAPHY*

E. E. STERNS**, *Kingston, Ontario*

Our investigations continue into the value of plate (liquid crystal) thermography in predicting the development of cancer of the breast, and indicating the prognosis of such cancers once they have been diagnosed. We have just completed a review of 695 breast-screened patients with follow-ups ranging from three to seven years. In this group 2495 thermograms were performed.

Two diagnostic parameters were measured in each thermographic examination. The first was the "diagnosis" classified as normal, equivocal or abnormal, based on differences in pattern and temperature between the two breasts. The second was thermographic "index", which was based on the overall breast temperature and vascular pattern. Three classes were defined: Type 1 — avascular low temperature, type 2 — intermediate, type 3 — high vascularity and high temperature.

Two-thirds of all thermograms performed were normal and 11% abnormal. The thermographic index demonstrated no association with benign or malignant lesions, or with any other parameters except that patients over the age of 60 had a low incidence of type 3 indices.

Forty-three patients (mean follow-up period 54 months) had 75% or greater incidence of abnormal and/or equivocal thermograms. One of these 43 patients was discovered to have a breast cancer after six clinic visits; during this period five thermograms were performed, all were either abnormal or equivocal. In the entire group (695 patients), only two others were found to have carcinoma during the follow-up period and both had a 50% incidence of abnormal thermograms.

The remaining patients have continued free of malignancy, both clinically and mammographically.

At this time the data do not suggest that thermography has a major role in predicting the development of cancer but one cannot discount the association of persistently abnormal thermograms in the three patients in whom the carcinoma was diagnosed.

Eighty-eight patients who had a thermogram before the diagnosis of breast cancer have been followed for a mean period of 32 months. Twenty-one per cent of these have developed metastases (mean disease-free interval of 22 months) and nine (10%) have died of their disease.

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*Project 417.

**Professor of Surgery, Queen's University, Kingston.

At this time there is no evidence that the thermographic "diagnosis" or the thermographic "index" bears a relationship to the prognosis. The prognostic value of thermography cannot be compared to that of estrogen receptor status, clinical and pathological staging, lymph node status and tumor size. The latter all demonstrate a relationship to the prognosis while thermography did not.

Our original report on the value of thermography in the diagnosis of breast cancer suggested that the procedure was of limited value. At this time our conclusions are that thermography does not effectively predict the development of cancer, or determine its prognosis.

HEMATOPORPHYRIN DERIVATIVE PHOTORADIATION THERAPY FOR CANCER*

J. C. KENNEDY**, *Kingston, Ontario*

We have evaluated the toxicity and clinical effectiveness of hematoporphyrin derivative (HpD) photoradiation therapy in the following patients: 19 with breast carcinoma; 7 squamous-cell carcinoma of the head and neck; 5 with malignant melanoma; 5 multiple primary basal-cell carcinomas; 2 with Kaposi's sarcoma; 1 each with carcinoma of the endometrium, ovary, cervix, anal canal, or lung; and 1 each with retinoblastoma or soft-tissue sarcoma. Eight patients with breast carcinoma and two with malignant melanoma were treated in collaboration with Dr. C. Tanser of the OCF Hamilton Clinic. All except those with basal-cell carcinoma had advanced disease and multiple metastases.

We did not detect any direct toxicity to injected HpD at any time, even in two patients who were given more than 20 injections over a period of several years. However, all patients developed skin photosensitivity to sunlight and to strong artificial light. This lasted for 1 to 14 weeks after injections, the most common duration being approximately 3 weeks. Repetition of an injection before the HpD from the previous injections had been cleared intensified the photosensitivity and extended its duration. Non-malignant tissue in treatment field previously exposed to tissue tolerance doses of ionizing radiation responded to photoradiation like non-irradiated tissue, if there was no visible evidence of damage before treatment. Tissues showing visible radiation damages, tissues that were inflammed for any reason, or fresh surgical scars were unusually susceptible to phototoxic damage. Patients who had been treated previously with Adriamycin showed unusual skin sensitivity and could develop cytotoxic skin reactions following doses of light that would have been quite safe for other patients.

Photoradiation therapy was most effective if the malignant tissue was in thin sheets or small nodules, contained little melanin, and had a long doubling time. Highly melanotic tumors, very thick tumors, and partially necrotic tumors did not respond as well. One breast carcinoma and one squamous-cell carcinoma showed intrinsic resistance to the treatment, but all others were susceptible to phototoxic destruction.

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*Project 441. (Continuation of Projects 352 and 369)

**Career Scientist, Ontario Cancer Foundation Kingston Clinic; and Associate Professor of Radiation Oncology and Pathology, Queen's University, Kingston.

IMMUNOCHEMICAL STUDIES ON TUMORS OF THE URINARY TRACT*

A. MORALES** and A. S. D. PANG†, *Kingston, Ontario*

The blood groups AB and H(O) are present in many normal tissues and their deletion has been associated with tumor development. M and N antigens, the second most important antigenic markers in the human blood group system are present in normal tissues but, partially or completely, are absent from the surface of neoplastic cells. The absence of the blood group antigens on the cell surface is due, at least in part, to their incomplete biosynthesis. It would be expected, therefore, that their precursors accumulate in such tumors. The immediate precursor of the M and N antigens is the T (Thomsen-Freidenreich) antigen, which normally is cryptic but can be exposed after treatment with neuroaminidase. The T antigen, however, appears spontaneously on the surface of neoplastic cells. In a manner similar to the expression of anti-A and anti-B antibodies, all humans beyond infancy possess anti-T antibodies.

We have conducted studies to determine the presence of T antigen on fresh and formalin-fixed samples of normal and neoplastic organs of the genitourinary tract. Studies have also been performed to establish the serum anti-T titers of normal individuals and patients with genitourinary cancer.

Immunofluorescent techniques applied to 80 tissue samples have demonstrated the presence of T antigen in over 50% of the malignant tissues while little or none is apparent in non-neoplastic tissues. Serological assessment of cancer patients suggests that they have a depressed anti-T antibody titer.

Although a sizable literature exists on the deletion of AB and H(O) antigens from abnormal tissues of the urinary tract, little is known about the M and N antigens and their precursors. A longer follow-up of cancer patients with low anti-T antibody titers and the correlation of T antigen presence in the original tumor with the degree of anaplasia may show that low titers are significant prognostic indicators.

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*Project 442.

**Professor and Chairman, Department of Urology, Queen's University, Kingston.

†Lecturer in Urology, Queen's University.

HUMAN NEURAL-CREST TUMORS – NEURONAL-GROWTH FACTORS*

R. J. RIOPELLE**, *Kingston, Ontario*

The role of serum neuronal-growth factors in the hereditary neural-crest neoplastic disorder, von Recklinghausen neurofibromatosis, has been studied by measuring, by biological assay, these factors in extracts of human serum. Serum samples from patients with carefully documented von Recklinghausen disease, as well as samples from unaffected relatives and non-related, non-affected persons, were assayed for growth-factor activity using a standardized sensory neuronal-cell-culture system developed to measure nerve growth factor (NGF)[1]. Factors released into culture media from neural-crest-derived tumors were assayed in a similar fashion.

Analysis of 87 specimens from 69 patients in 48 families with von Recklinghausen disease, plus 16 samples from comparison subjects indicates that neuronal-growth-factor activity is heterogenous and does not distinguish von Recklinghausen patients from unaffected patients. NGF activity in extracts, as measured by anti-NGF antibody inhibition of extract-induced nerve growth, is present in very small amounts and does not differ in the various patient groups studied.

In related preliminary studies, it has been shown that human tumors of neuronal-crest origin – neurofibroma, melanoma, neuroblastoma – release bioassayable neuronal-growth factors in culture. Cell lines from melanoma and neuroblastoma tumors also bear cell-surface receptor for NGF[2], and one of these cell lines (MeWo) shows enhanced growth in NGF-treated, tumor-bearing, immune-deprived mice.

Levels of circulating neuronal-growth factors, as detected by biological assay, do not contribute to the identification of von Recklinghausen neurofibromatosis patients.

Human tumor cells of neural-crest origin do produce neuronal-growth factors and can respond to some of these factors. Studies of local production of, and response to, growth-promoting factors by neural-crest-derived tumors may offer an approach to trophic-factor manipulation of this type of tumor in humans.

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*Project 443.

**Associate Professor of Medicine (Neurology), Queen's University, Kingston.

Ontario Cancer Foundation London Clinic

INVESTIGATION OF PHYSICAL RADIATION PARAMETERS*

D. J. DAWSON**, *London, Ontario*

The beam penumbra for ^{60}Co, 6MV and 31MV x-rays from an AECL Theratron 780, an AECL Therac 6 and a Brown Boveri betatron are being investigated. The measurements have been undertaken by Mr. A. C. Akinradewo, a graduate student in the Department of Physics at the University of Western Ontario in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

The measurements have involved the use of specially-designed ionization chambers with buildup caps to produce electronic equilibrium. The wall materials and inside diameters of the chambers have been varied to consider the effect of density and chamber dimensions on the measured penumbral widths.

The results have been interpreted in the light of a recently proposed model, which considers that two distributions exist in the penumbral region of high-energy therapy units, namely, the photon fluence distribution and the dose distribution. The differences between these two distributions are stongly dependent on beam energy and are associated with the lateral spread of the secondary electrons. It has also been determined that the dosimeter characteristics determine which distribution is being measured.

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*Project 266.

**Senior Physicist, Ontario Cancer Foundation London Clinic; and Associate Professor of Therapeutic Radiology, and Sessional Lecturer of Physics, University of Western Ontario, London.

COMBINED MODALITY TREATMENT OF CANCER USING MULTICELL SPHEROIDS AND TRANSPLANTED TUMORS IN MICE*

W. R. INCH** and E. R. STROUDE†, *London, Ontario*

Mammalian cells, which normally grow as a monolayer culture on Petri dishes, can be placed in spinner culture and grown as multicell spheroids. Spheroids are three-dimensional structures simulating the growth and microenvironment of tumors and micrometastases.

We have investigated the effect of the chemical lucanthone hydrochloride (Miracil D) on monolayer and spheroid cultures of Chinese hamsters V79-171b cells. The growth medium was Eagles basal medium containing Hank's salts and supplemented with 13% fetal bovine serum. Miracil D concentrations were 4, 10 and 100 μM and exposure times were up to six hours. The chemical was highly toxic to V79 monolayer cultures in the exponential phase of growth. At a concentration of 100 μM, survival was decreased to 42% of the initial value after 1.5 hours and all cells were dead by 5.5 hours.

Survival of the cells in spheroids (550 μ diam.) following Co^{60} radiation was determined by giving graded doses to a maximum of 35 Gy. The combined radiation-chemical studies were carried out using 20 μM concentration, which was not cytotoxic for up to three hours exposure; actual pre-irradiation exposure was one hour. These experiments showed no difference in survival between the control and treated spheroids.

Miracil D (20 μM) also was investigated in combination with the radiation-sensitizing chemical, desmethyl misonidazole (Ro-05-9963) (2.0 mM). Both chemicals were added one hour before radiation exposure. It was found that Ro-05-9963 increased the radiosensitivity of cells in the spheroid. D_0 values were 4.9 Gy for control spheroids and 2.5 for treated spheroids, giving a dose-modifying factor of about 2.0. The presence of lucanthone did not alter the radiosensitizing effect of Ro-05-9963. Therefore we conclude that lucanthone is not a useful adjunct to radiotherapy as a means of increasing tumor cell killing. Olive and Durand[1] have shown similar toxicity for monolayer cultures, and Bases[2] has shown a significantly greater cell kill by x-rays in HeLa cells exposed to 3.0 μgm/ml Miracil D for four hours.

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*Project 393.

**Experimental Oncologist, Ontario Cancer Foundation London Clinic; and Professor of Radiation Oncology and Biophysics, University of Western Ontario, London.

†Research Assistant, OCF London Clinic.

SURFACE ANTIGENS OF CULTURED HUMAN ASTROCYTOMAS: IDENTIFICATION AND INTERPRETATION OF SUBSETS*

J. G. CAIRNCROSS**, *London, Ontario*

Insights into tumor biology have emerged as a consequence of studies of tumor cell phenotypes and the phenotypes of the normal counterpart at different stages of development. For example, it is now possible to subtype acute lymphoblastic leukemia on the basis of differentiation antigens. The precise relationship between the leukemic cell, the normal cell of similar phenotype, and the target cell for malignant transformation is an area of active investigation. Surprisingly little attention has been given to an analysis of relationships between astrocyte differentiation and the phenotypic characteristics of astrocytomas. It is conceivable that a sophisticated serological classification of neural tumors would provide important insights into brain-tumor biology and, at the same time, have clinical impact in the areas of diagnosis, prognosis, treatment selection, etc. To this end the surface antigens of cultured human malignant astrocytomas are being analyzed using mouse monoclonal antibodies. The initial phases of this project are now described.

BALB/c mice were immunized repeatedly with either SK-MG-1 (a glial fibrillary acidic protein (GFA)-negative astrocytoma line) or SK-A02 (a GFA-positive astrocytoma line). After fusing the spleen cells of the immunized mice with NS/1 mouse myeloma cells, 12 antibody-producing hybrids were selected for detailed study.

Serological analysis permitted the identification of nine distinct antigenic systems. Four monoclonal antibodies identified cell-surface antigens preferentially expressed on tumors of neuroectodermal origin, and these antibodies subdivided a large panel of cultured astrocytomas into distinguishable subsets. These restricted antigenic systems had a restricted distribution on normal cells as well. Cell-surface determinants present only on tumor cells were not detected in this analysis. Of particular interest were the two surface antigens designated, A010 and AJ8, because they showed mutually exclusive expression on the astrocytoma panel. 4/7 A010-positive astrocytomas expressed GFA, an astrocyte differentiation antigen expressed in the mature normal cell, whereas all AJ8-positive astrocytomas (9/9) were GFA-negative.

The division of cultured astrocytomas into mutually exclusive A010-positive and AJ8-positive subsets and the relationship between the A010/AJ8 surface phenotype and GFA expression provide an opportunity to speculate on the biological significance of these cell surface markers and of the subsets they define. The intriguing feature of A010 and AJ8 expression is the essentially non-overlapping distribution on cultured astrocytomas. It is unlikely that subsetting of this kind is explained by a random expression or loss of the A010 and AJ8 determinants. However, this reciprocal relationship could be taken as evidence for the existence of two antigenically distinct astrocyte lineages or two antigenically distinct phases in a single lineage. Past studies of GFA have indicated that GFA is absent in early astrocyte precursors, detectable in all mature astrocytes, absent in highly anaplastic astrocytomas and detectable in well-differentiated tumors. The observations that A010 is present on GFA-positive cultured astrocytomas and that AJ8-positive tumors are GFA-negative suggest that the surface markers reflect the state of differentiation of astrocytomas in culture and lends support to the latter view that these determinants are differentiation antigens and markers for early and late stages of astrocyte development. Serological typing for AJ8, A010 and GFA suggests that cultured astrocytomas can be divided into three groups on the basis of differentiated-related phenotypic characteristics (Fig. 1).

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*Project 471.

**Neuro-oncologist, Ontario Cancer Foundation London Clinic; and Assistant Professor of Radiation Oncology, University of Western Ontario, London.

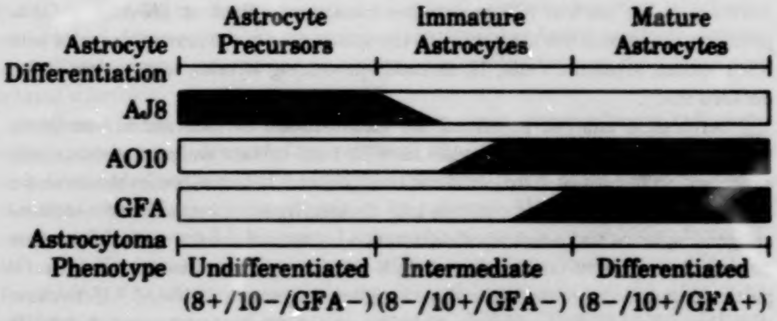
Astrocyte Precursors
Immature Astrocytes
Mature Astrocytes
Astrocyte Differentiation
AJ8
AO10
GFA
Astrocytoma Phenotype
Undifferentiated (8+/10−/GFA−)
Intermediate (8−/10+/GFA−)
Differentiated (8−/10+/GFA+)

Fig. 1. Proposed relationship between astrocyte differentiation and phenotypic characteristics of cultured astrocytomas, based on serological typing for AJ8, A010, and GFA.

Future studies will focus on the production of antibodies to other astrocyte differentiation antigens, techniques to grow normal non-human astrocytes and their precursors, and lastly serological typing of fresh tumor tissue using these reagents.

ADDITIONAL INVESTIGATIONS

In addition to the research projects being conducted at the Ontario Cancer Foundation London Clinic, for which grants have been approved, Dr. Haydn Bush, Director of the London Clinic, reports on the following clinical research investigations:

PROGNOSTIC FACTORS AND NMR IN THE LYMPHOMAS

Supported by the Ministry of Health, Dr. J. Skillings is evaluating the role of NMR scanning in the assessment of abdominal disease in non-Hodgkin's lymphoma and Hodgkin's disease. A retrospective review of patients with non-Hodgkin's lymphoma has been done to assess prognostic factors. This study analyzes the effect of patient characteristics on survival using Cox regression analysis. We are continuing to participate in the NCIC study of escalated BACOP-Septra in the management of patients with poor-prognosis, non-Hodgkin's lymphoma.

NMR AND LUNG DAMAGE

With the support of the Medical Research Council and in association with Dr. F. S. Prato, Dr. W. R. Inch is applying nuclear magnetic resonance to evaluate damage to lung produced by certain chemotherapeutic agents and radiation.

BASIC NMR SPECTROSCOPY STUDIES

With Drs. Sharp and Peemoeller, Dr. Inch is using formal two-dimensional NMR to monitor the relaxation parameters in normal, preneoplastic and neoplastic systems. This study will help to clarify the potential of NMR in studies of cancer.

RADIATION AND CATARACT

In association with Dr. Trevithick of the University of Western Ontario, Dr. Inch will evaluate the causes of cataract formation.

SPHEROIDS, HYPOXIC CELLS AND CYTOTOXIC DRUGS

Studies are continuing into the biology of hypoxic cells and the diffusion of cytotoxic drugs into multicell spheroids.

HUMAN MONOCLONAL ANTIBODY STUDIES

In this laboratory, Dr. J. S. Gardner, a Terry Fox Fellow, is applying techniques of human-human hybridomas, which have been established using lymphocytes from cancer patients with a human hybridoma cell line. Frequency rates of $1:10^3$ to $1:10^4$ have been obtained with prestimulation of patients' lymphocytes with Epstein-Barr virus before fusion.

Current research is focussing on the optimization of screening techniques to identify useful human monoclonal antibodies in human breast and ovarian cancers.

Panels of monoclonal antibodies are being developed for in vivo and in vitro diagnostic tests and, thereafter, these may have potential in the therapy of human tumors.

REVERSIBLE SYNCHRONIZATION OF NORMAL PROLIFERATING CELL POPULATIONS

Drs. W. I. Kocha and H. Bush have created a model for head and neck squamous cell carcinoma using DMBA-painted, golden-hamster cheek pouches. The distribution of cells within the cell cycle has been determined for golden-hamster bone marrow. Preliminary data have been obtained on the effects of some chemotherapeutic agents on blocking marrow cells into G_1 phase thereby protecting them for S-phase-specific agents. Further investigations are being done to determine whether marrow protection will allow an increase in the doses of phase-specific agents with consequent improved responses of tumors not so readily synchronized.

NEURO-ONCOLOGY RESEARCH

This year, Dr. D. Macdonald and his colleagues in clinical neuro-oncology are conducting large retrospective study of patients presenting with primary brain tumor to medical school centres in London, the London Clinic and its referral region. This study, which involved 1600 patients with central nervous system tumors over a 10-year period, will attempt to evaluate prognostic factors in relation to the natural history of these diseases.

Other studies are planned of meningela cancer, and of the addition of chemotherapy to radiation in the treatment of cerebral metastases.

Studies of tumor-cell phenotypes and the phenotypes of the normal counterpart at different stages of development have yielded considerable insight into tumor biology. The surface antigens of cultured human malignant astrocytomas and cultured normal mouse astrocytes are being analyzed using mouse monoclonal antibodies. Observations to date suggest that cultures of human astrocytomas can be subgrouped on the basis of a differentiation-related, cell surface antigenic profile. Currently, Dr. J. G. Cairncross is developing techniques for growing normal nonhuman and human astrocytes and their precursors and is analyzing the effects of differentiation promoters on human astrocytomas. Future studies will focus on the production of a second generation of mouse monoclonal antibodies to astrocyte differentiation antigens, and the serological typing of fresh tumor tissue with these reagents. In the future, this work may give rise to a sophisticated immunopathological classification of astrocytomas analogous to that of the hematopoietic and lymphoid malignancies.

TUMOR PROGRESSION AND METASTASIS

The major area of research in the experimental oncology laboratory is the somatic cell genetics of tumor progression and metastasis using two different in vivo model systems. The first model — the embryonic chick, which evaluates growth of micrometastasis following cell release into the circulation — offers a convenient and rapid alternative to current models. Dr. A. F. Chambers has shown that the advantages of this sytem include measurement of initial cell response to foreign tissue (growth or death) rather than the long-term ability to form a tumor. Because of this model's immature immune system, it can test cells from a variety of species. An additional property relates to the chick's tolerance to a range of temperatures; thus it can be used to test temperature-sensitive mutants and variants.

Work continues in collaboration with Drs. J. F. Harris, R. P. Hill and V. Ling, which employs the experimental metastasis/mouse system. This work has important implications for the isolation of pure populations of metastatic variants and it may help us explain the differences encountered in attempts to identify tumor-cell markers unique to metastatic cells.

Ontario Cancer Foundation Ottawa Clinic

EASTERN CO-OPERATIVE ONCOLOGY GROUP*

W. E. HIRTE**, L. L. STOLBACH**, C. CRIPPS‡, V. YOUNG‡,
D. PERRAULT‡, G. E. CATTON†, C. DANJOUX‡, R. McDERMOT‡,
J. BORMANIS‡, A. U. HAQ‡, E. LIEPA‡, R. BARR‡, M. ORIZAGA‡,
J. A. MAROUN‡, D. J. STEWART‡, P. DROUIN‡, S. LEGAULT-POISSON‡
and R. POISSON‡

The Eastern Co-operative Oncology Group — a multidisciplinary, multi-institutional organization, is devoted to the study and treatment of neoplastic disease. This group was established to improve cancer therapy through effective clinical trials. Its basic premise is that co-operative studies will lead more rapidly and effectively to the control and cure of cancer and, thus, provide better patient care.

The Group is made up of surgeons, pathologists, radiotherapists and medical oncologists from the 29-member institutions, who are involved in combined modality studies. There are 46 Group-wide Phase II-III studies and 27 active pilot studies. In the past two years the Ottawa Group has entered 90 patients into the various studies.

Representatives from the Ottawa Clinic participate in regular semi-annual meetings of the Group to discuss current and proposed studies and to contribute to decisions regarding these. Dr. W. E. Hirte is a member of the Genitourinary Steering Committee; Dr. M. C. Cripps, the Head and Neck Steering Committee; Dr. J. A. Maroun, the Immunology and New Agents Committee; and Dr. D. J. Stewart is a member of the New Agents Steering Committee and chairman of the Pharmacology Subcommittee.

As it has evolved, this program has led to an improvement in both quality and quantity of clinical research. Key steps in the development of new treatments or therapeutic modalities have been: (1) The availability of adequate research resources; (2) the input of new ideas by individual investigators; (3) scale-up and confirmation or refutation of results of pilot studies; and (4) throughout this process, comparison of promising new treatments with existing standard treatments.

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*Project 267. (Final Report)

**Co-Principal Investigators.

†Senior Investigator.

‡Collaborators from Department of Medical and Radiation Oncology, Ontario Cancer Foundation Ottawa Clinic; Department of Medicine, University of Ottawa; and Ottawa Civic Hospital, Ottawa General Hospital and Hôpital Saint-Luc, Montreal.

Information regarding advances in treatment is communicated to local resident and consulting staffs, to the National Cancer Institute of Canada and the Cancer Research Co-ordinating Committee.

Participation in the Eastern Co-operative Oncology Group will continue through support from other sources.

ADDITIONAL INVESTIGATIONS

Dr. G. E. Catton, Director of the Ottawa Clinic, reports on the following clinical research investigations:

BREAST CANCER

- Drs. R. S. R. McDermot and J. E. Devitt are contributing to the NSABP protocols for the evaluation of segmental mastectomy (with and without radiotherapy) versus total mastectomy in Stage I breast cancer, and to the addition of adjuvant chemotherapy to these modalities in Stage II breast cancer.
- Drs. W. E. Hirte, L. L. Stolbach, C. Cripps, D. Perrault, D. Stewart and J. A. Maroun are contributing patients to NSABP protocols to determine the effect of adjuvant chemotherapy and hormonal therapy in breast cancer patients according to age of patient, stage of disease, and estrogen and progesterone receptor status. These studies include both node-positive and node-negative patients.

NATIONAL TRIALS

The Ottawa Clinic particpates in the following studies of the National Cancer Institute of Canada and the Cancer Research Co-ordinating Committee:

- Adjuvant immunotherapy in early melanoma.
- Treatment of Stages I and IIa high risk, or Stages IIb or IIIo carcinoma of the ovary after total hysterectomy and bilateral salpingo-oophorectomy.
- Adjuvant immunotherapy in resected bronchogenic carcinoma.
- Treatment of advanced ovarian carcinoma.
- Phase II chemotherapy of advanced colorectal carcinoma.
- Treatment of plasma-cell myeloma with chemotherapy.
- Treatment of limited small cell carcinoma of the lung.
- Treatment of poor prognosis non-Hodgkin's lymphoma with chemotherapy.

EASTERN CO-OPERATIVE ONCOLOGY GROUP

The Ottawa Clinic has continued to contribute to the Eastern Co-operative Oncology Group in the following areas: Participation in group meetings; membership in Site and Modality Steering Committees; and in patient accrual.

LOCAL CLINICAL TRIALS

- Cisplatin plus cytosine arabinoside with and without caffeine for glioblastomas, and head and neck carcinoma.
- Metronidazole plus chemotherapy for a variety of tumors.
- Biochemically-sequenced methotrexate and 5-fluorouracil for a variety of neoplasms.

- Intracarotid infusion of BCNU, cisplatin, VM-26 for intracerebral tumors.
- Intrathecal methotrexate, cytosine arabinoside, hydrocortisone plus thio-TEPA for meningeal involvement by malignancies.
- Intra-arterial cisplatin with and without disulfiram for localized bladder carcinoma.
- Treatment of advanced prostate carcinoma with flutamide.
- Double blind trial of Vitamins E and C versus placebo as protectors against doxorubicin cardiotoxicity.

PHARMACOLOGY STUDIES

The following studies are being conducted in the Cancer Research Laboratory at the Ottawa General Hospital:

- Plasma pharmacokinetics of VM-26, VP-16, mitomycin-C and tiazofurin.
- Human, autopsy-tissue distribution of chemotherapy agents and their metabolites — VM-26, VP-16, Adriamycin, vincristine, bleomycin, cytosine arabinoside, mitomycin-C, metronidazole, cyclophosphamide, methotrexate, 5-FU, lonidamine and cisplatin.
- Penetration of antineoplastic agents — VP-16, VM-26 with and without glycerol, and cytosine arabinoside into intracerebral tumors.
- Bioavailability of oral VP-16.
- Relationship of plasma and tissue pharmacology of cisplatin to cisplatin-induced nephrotoxicity.

University of Ottawa

STUDIES ON POLYAMINE AND CYCLIC NUCLEOTIDE METABOLISM IN CANCEROUS PROSTATE*

R. L. SINGHAL**, *Ottawa, Ontario*

Polyamines, cyclic nucleotides and glutathione have been recognized as important growth factors in biological systems. There is also a relationship among polyamines, cyclic adenosine monophosphate (AMP) and testicular hormones with respect to the growth of the prostate glands. The present investigation was undertaken to define more clearly the role of polyamines, glutathione and cyclic AMP-adenylate cyclase system in abnormal growth of the prostate. Earlier, we had demonstrated the involvement of cyclic AMP in androgen action in the prostate while the other nucleotide, cyclic glutamic monophosphate (GMP) was not affected. The levels of the three polyamines, i.e. putrescine, spermidine and spermine and the activity of the two synthesizing enzymes i.e. 1-ornithine decarboxylase and S-adenosyl-1-methionine decarboxylase were measured in both normal and squamous cell carcinoma of the prostate after a variety of hormonal manipulations. Gonadectomy significantly lowered the levels of the three polyamines and reduced the activity of the two enzymes. Testosterone replacement restored the values of the polyamines and the activity of the enzymes to near-normal levels. Significantly lower amounts of polyamines were detectable in tumor tissue than in the control prostate.

The above studies were extended to the determination of the levels of reduced and oxidized glutathione and the activity of its metabolizing enzymes during normal and abnormal growth of the prostate. Castration for seven days produced a significant decrease in the concentration of reduced glutathione and in the activities of glutathione reductase, superoxide dismutase and glutathione peroxidase. The replacement of testosterone in castrated animals for seven days elevated all these parameters to almost normal values. The levels of reduced glutathione and the activity of its metabolizing enzymes were identical in tumors implanted in normal and castrated animals. The prostatic tumor showed considerably higher activity of glutathione reductase and a lower activity of glutathione peroxidase compared to the normal tissue.

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*Project 421.

**Professor of Pharmacology, School of Medicine, University of Ottawa.

The work carried out on this project has demonstrated that polyamines and glutathione metabolism, and activity of the adenylate cyclase-cyclic AMP system display androgen dependency in the normal prostate. Our data further suggest that the above growth factors are not affected by androgen treatment of the prostatic squamous-cell carcinoma. The alterations observed in tumor tissue in the activity of glutathione reductase, glutathione peroxidase and superoxide dismutase may be significant in respect to the rapid and abnormal growth of the ventral prostate.

Ontario Cancer Foundation Thunder Bay Clinic

STUDY OF POSTRADIATION CHANGES IN LUNG USING COMPUTERIZED TOMOGRAPHY*

J. F. KOTALIK** and P. D. SHARMA†, *Thunder Bay, Ontario*

The goal of the study is to determine the pattern of change of lung density after radiation of lung in man, and to detect any correlation, which may exist, between the lung density and radiation dose. We calculated the density of lung from CT numbers generated by EMI-7070 scanner located at McKellar General Hospital.

In this initial phase of the study our main concern was methodology: in this connection we have examined reproducibility and variability of these measurements using both patients' data and that from a phantom. Preliminary results suggest that we can achieve statistical validity. The study now includes eight patients — two were radiated for bronchogenic carcinoma while the other six were treated for carcinoma of the breast. About 1500 scans were analyzed. Observations for a one-year period shows significant variation in lung density and total lung volume. The significance of these changes in time, relationship to dose and changes in frequency distribution of certain lung densities are all the subject of current investigations.

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*Project 462.

**Director, Ontario Cancer Foundation Thunder Bay Clinic.

†Medical Physicist, Ontario Cancer Foundation Thunder Bay Clinic.

Hospital for Sick Children, Toronto

HETEROGENEITY OF ACUTE LYMPHOBLASTIC LEUKEMIA OF CHILDHOOD

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Over the last three decades, the approach to childhood acute lymphoblastic leukemia (ALL) has undergone considerable change. New forms of therapy have produced dramatic improvements in survival and now almost 50% of children with ALL do survive. Before addressing the question of failure of treatment in this disease, one must consider its heterogeneity, the need for better methods of probing this heterogeneity and hopefully identify better criteria for the identification and classification of leukemia.

To these ends, we have developed the technology to quantitate and directly compare the number of specific antigenic sites on the surface of these leukemic cells. Our results clearly identify the heterogeneity of the common form of childhood ALL, based on the quantitation of Ia and CALLA sites. In addition, this heterogeneity is complemented by differing abilities to stimulate in a mixed lymphocyte reaction and the response to tetradecanoyl phorbol acetate.

We have in progress a prospective study of more than 40 patients to determine if these parameters have prognostic and therapeutic significance for the management of leukemia.

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*Project 397.

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INTERMEDIATE FILAMENT PROTEINS AS MARKERS IN PEDIATRIC MALIGNANCIES*

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Intermediate filaments, microfilaments and microtubules are the major constituents of the cytoskeletal system of cells. We prepared antibodies against four of the classes of intermediate filaments — cytokeratin, vimentin, desmin and neurofilament, and purchased antibody to glial fibrillary acidic protein. Such reagents are extremely useful in surgical pathology as adjuncts in the diagnosis of undifferentiated neoplasms. Cytokeratin was purified from skin, vimentin from cultured human fibroblasts, desmin from chicken gizzard and neurofilaments from pig brain. These polypeptides were injected into rabbits and antibodies were obtained.

By immunofluorescence and immunoperoxidase techniques, it has been demonstrated that different types of neoplastic tissue stain positively with antibodies to intermediate filaments, i.e. anticytokeratin stains neoplasms derived from epithelium; antivimentin, neoplasms of mesenchymal and vascular tissue; antidesmin, neoplasms derived from muscle; antineurofilament, neoplasms involving neurones; and anti-GFAP, neoplasms of glial cells.

Pediatric neoplasms were categorized using the anticytokeratin and antivimentin antibodies[1]. All epithelial neoplasms stained for cytokeratins but not for vimentin. In contrast, tumors of mesenchymal or lymphoid origin were positive with the antivimentin antibody, but did not stain with the anticytokeratin antibody. Rhabdomyosarcomas derived from skeletal muscle were positive with the antidesmin and with other antibodies possessing specificity for constituents of muscle cells[2].

All of these antibodies were extremely useful in establishing or confirming the diagnosis of various types of pediatric neoplasms.

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Ontario Cancer Foundation Toronto-Bayview Clinic

GENERATION OF SPONTANEOUS KILLER CYTOTOXICITY (SKC) DURING CULTURE OF CELL SUBPOPULATIONS DEPLETED OF SKC*

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Human spontaneous killer cells (SKC) mediate cytotoxicity against certain tumor cells without prior sensitization. Little is known about precursor cells of SKC. Observing that subpopulations of human peripheral blood lymphocytes lacking SKC could generate SKC during culture, we sought to determine whether this culture-induced cytotoxicity resulted from the maturation of SKC precursor cells.

Human peripheral blood lymphocytes were purified by the removal of other blood-cell elements on a Ficoll-Hypaque gradient and on plastic Petri dishes. Then lymphocytes were separated further on a Percoll density gradient. Whereas SKC was enriched among lower density cells, higher density cells contained little or no SKC, as has been previously described[1].

Striking increases in SKC were observed among high-density cell fractions during culture for 2-3 days in standard culture medium containing fetal calf serum. This activity persisted for at least six days, whereas SKC within lower-density fractions decreased during this same period. This culture-induced cytotoxicity was not due to suppressor-cell depletion during cell separation because the same result was obtained from cells cultured before separation. We observed newly evolved, lower-density cells among higher-density cell fractions after culture and these cells mediated significant levels of SKC. Cultured, higher-density cells showed increased responsiveness to interferon, which suggested that culture-induced cytotoxicity results from recruitment of precursor cells to mature cytotoxic cells as has been suggested by others[2]. Irradiation of higher-density cells before culture abolished culture-induced cytotoxicity.

We conclude that SKC can be generated from SKC-depleted, higher-density cell populations of human peripheral blood. This cytotoxicity requires cell proliferation and probably results from the recruitment and differentiation of interferon-sensitive precursor cells to mature effector cells. We are working to characterize the morphological and biological properties of both precursor and effector cells. In the future we hope to test the ability of peripheral blood lymphocytes of SKC-deficient cancer patients to produce culture-induced cytotoxicity. We will determine whether various levels of this cytotoxicity may predict patients' response to therapeutic agents such as interferon.

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*Project 468.

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CLINICAL INVESTIGATIONS

Dr. R. D. T. Jenkin, Director of the Toronto-Bayview Clinic, reports on the following clinical research investigations:

COMBINATION CHEMOTHERAPY IN NON-SMALL-CELL LUNG CANCER

Dr. David Osoba is conducting Phase II clinical trials to determine the value of bleomycin, cis-platinum and etoposide (VP-16) in non-small-cell lung cancer. In the first study, 53 patients with recurrent or extensive disease received these drugs and had an overall response rate of 45%. The response rate in the squamous and large-cell subtypes is 55% and for adenocarcinoma 20%. It is too early to determine whether this approach improves survival. In the second study, patients with "limited" squamous-cell carcinoma receive up to two cycles of treatment with bleomycin, cis-platinum and etoposide followed by radiation. The object of this study is to determine the response rate to chemotherapy in previously untreated squamous-cell lung cancer and to discover combined modality therapy associated with unexpected or increased toxicity.

INTRAPERITONEAL CHEMOTHERAPY FOR OVARIAN AND COLORECTAL CANCER

Dr. I. J. Kerr has initiated two clinical-pharmocologic studies using high volume intraperitoneal chemotherapy in selected patients with intra-abdominal metastatic ovarian and colorectal carcinoma. Drugs being studied include aclarubicin (Phase I) and 5-FU (Phase II).

MELANOMA

Dr. N. Iscoe has reviewed 108 patients with malignant melanoma to assess the value of diagnostic and staging investigations in the initial examination and follow-up of this disease. This data will be combined with similar information from the Princess Margaret Hospital for further analysis.

NATURAL KILLER CELLS

Natural killer cells may play an important role in the body's defences against cancer. Dr. J. J. Rusthoven is studying the mechanisms by which the destruction of tumor cells by natural killer cells is altered during culture. This study may lead to clinically useful improvements in the eradication of tumor cells by the patient's own natural killer cells.

PSYCHOSOCIAL ASPECTS OF CANCER

The Psychosocial Research Group is developing a questionnaire, which it hopes will predict the development of anxiety and depression in patients with cancer. Initial reliability testing has been done and the questionnaire's format and content are being modified as a result of this initial test.

BREAST CANCER

Dr. D. J. A. Sutherland continues his analysis of steroid receptor assays in patients with breast cancer (currently in excess of 10,000 patients), as well as studies of plasminogen-activating activity as a marker of hormone activation in human tumors and especially in breast cancer. Clinical studies in breast cancer, particularly a comparative trial on the effects of megace and tamoxifen, are in progress. Dr. Sutherland is also investigating the influence of several endocrinopathies on sex-hormone-binding globulin.

CO-OPERATIVE CLINICAL TRIALS

Patients are being entered into several NCIC clinical trials: melanoma, small-cell lung cancer, non-Hodgkin's lymphoma, mesothelioma and control of chemotherapy-induced nausea and vomiting. Other trials include combined modality therapy in advanced head and neck cancer, and bisantrene in hypernephroma.

EWING'S SARCOMA

Dr. M. P. Berry has reviewed the recent experience in Toronto with this tumor, particularly with regard to a pilot study of the addition to adjuvant chemotherapy of sequential half-body radiation.

EFFECTS OF NITROAROMATIC RADIOSENSITIZERS ON RADIOLYTIC OXYGEN DEPLETION IN MAMMALIAN CELLS AND IN AQUEOUS SOLUTION

Dr. H. B. Michaels is developing a radiation-chemical model to elucidate the mechanism for the complex inter-related processes of radiolytic oxygen depletion and the reduction chemistry of nitroimidazoles at low concentrations of oxygen. The radiation-sensitizing drugs — misonidazole and metronidazole — interfere with radiation-chemical oxygen depletion and protect oxygen from depletion in mammalian cells irradiated at ultra-high-dose rates, in addition to their action as radiosensitizers of hypoxic cells. Parallel experiments in aqueous solutions of sensitizers are in progress.

THE OXYGEN DEPENDENCE OF THE REDUCTION OF NITROIMIDAZOLES IN A RADIOLYTIC MODEL SYSTEM

In collaboration with Dr. A. M. Rauth at the OCI and Dr. R. McClelland at the University of Toronto, Dr. H. B. Michaels is studying the mechanism responsible for the inhibition of nitroreduction of nitroimidazole radiation sensitizers by low levels of oxygen. In hypoxic mammalian cells, the nitroreduction in the cell of drugs such as misonidazole produces an active cytotoxic metabolite. This process is very sensitive to oxygen, which, if present even in micromolar concentrations, can prevent nitroreduction and protect the cells against the toxic effect, and may be important in vivo.

INCREASED RADIOSENSITIVITY OF AEROBIC MAMMALIAN CELLS FOLLOWING PRE-INCUBATION WITH MISONIDAZOLE IN HYPOXIA

Dr. Michaels has shown that incubation of cells in hypoxia with the radiosensitizer misonidazole increases the radiation sensitivity of these cells when subsequently irradiated in air. Radiosensitizers usually are active only on hypoxic cells. Given the possibility that a diffusible toxic product is produced during nitroreduction of the sensitizer, it now appears that toxicity of nitroimidazoles, generally perceived to be important only in hypoxic cells, also may be important in the radiosensitivity of non-hypoxic cells in tumors.

PHYSICS MEASUREMENTS ON THE THERAC-25 LINEAR ACCELERATOR

Mr. P. F. O'Brien and the clinical physics staff are determining the radiation-beam characteristics of the photon and electron modes of the new Therac-25. Mr. O'Brien and Dr. Michaels have undertaken radiation protection studies on the Therac-25, specifically measuring the transmission of neutrons through concrete, wood and polyethylene. The data were used to design a new shielding door for the Therac-25 room.

DEVELOPMENT OF A MICROCOMPUTER-ASSISTED, PATIENT-CONTOUR-TAKING DEVICE AND COMPENSATOR DESIGNING APPARATUS

The clinical physics staff have designed a system, presently being constructed in the machine shop and electronic shop, which will enable the physicist or dosimetrist planning radiotherapy to obtain information about patient contours quickly and accurately. The apparatus consists of sensors to identify position co-ordinates on the patient's skin, which then are processed by a microcomputer to display the contour. The information is coded in digital form and can be used in the design of tissue compensators for radiotherapy.

CLINICAL PHYSICS TECHNICAL DEVELOPMENT PROJECTS

These projects include the development of a thermoluminescent dosimetry (TLD) system; a new technique for radiation of breast cancer, technical improvements in the design of x-ray film cassettes for taking check films on treatment units, and an apparatus for accommodating patients for half-body radiation on the Therac-6.

Ontario Cancer Institute incorporating the Princess Margaret Hospital, Toronto

THE VALUE OF LOCAL OR REGIONAL RADIATION IN EARLY HODGKIN'S DISEASE*

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This study was begun in 1967. The specific aim was to explore, in patients with localized Hodgkin's disease (Stages I and II), the relative merits of irradiation to local involved region (IF – involved field) vs irradiation to the local region plus irradiation to the surrounding clinically uninvolved area (EF – extended field).

Between April 1967 and April 1973, 460 patients were entered on this study, 73 of whom came from the Princess Margaret Hospital in Toronto. In 1983 they will be eligible for the calculation of 10-year survival. Two-hundred and twenty patients received involved field treatment and 240 extended field. The present actuarial survivals are 85% for involved field and 87% for extended field at five years. Extension-free survival was significantly better in the EF group than in the IF within two years after treatment and that benefit persists to the current follow-up with extension-free survival of 42% IF and 64% EF at five years.

Six cases of leukemia have been reported in this series among whom less than one case would be expected at general population rates. All leukemias have occurred in 167 patients who required chemotherapy for extension of Hodgkin's disease after initial radiotherapy, implying an increased risk following chemotherapy of more than 200-fold.

While no significant effect of treatment on survival is seen when the total series is examined, a dissection of the population into a large number of subgroups shows equal and opposite treatment effect for the two sexes with a significant favorable effect of the extended field regimen in males and a non-significant unfavorable effect in females. Favorable survival is significantly correlated with initial characteristics of female sex, age under 40, and histologic type of nodular sclerosis or lymphocyte predominance. Histologic type is the most powerful predicator in the total series but its prognostic value is not seen in patients staged by laparotomy. One other potentially prognostic variable, mediastinal involvement, was investigated.

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*Project 181. (Final Report)

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There was no significant effect of mediastinal disease in any of the subgroups tabulated.

In the IF group, 40 deaths have occurred due to Hodgkin's disease and treatment and 17 to intercurrent disease. In the EF group, 37 deaths have occurred from Hodgkin's disease and treatment and 14 from intercurrent disease. Intercurrent disease has included infection, malignant disease, benign tumor, cardiovascular disease, pulmonary infarction, pulmonary embolus, cirrhosis, pneumonia, accidents, suicide and complications of surgery.

While the end point of this study is survival for those patients whose initial treatment was IF or EF, we are also studying patterns of relapse in the two groups, complications of treatment, complications of the disease and treatment, and salvage after relapse.

This study now is being supported by an NCIC grant.

RETINOBLASTOMA AS A MODEL FOR TUMOR-HOST INTERACTIONS*

B. L. GALLIE**, *Toronto, Ontario*

Studies of DNA transfer from human tumors to mouse fibroblasts have suggested that dominant mutation in a gene is important in oncogenesis. The difficulty with this model is the implication that a single mutation can lead to malignant disease, whereas previous data indicated that multiple events were required for malignant transformation. On the basis of our work in retinoblastoma we propose a model for tumorigenesis in which the essential element is loss of both copies of a regulatory gene. Loss of regulation then leads to uncontrolled proliferation with progressive karyotypic rearrangements.

The gene predisposing to the hereditary tumor, retinoblastoma, has been mapped to chromosome 13q14 by linkage to the enzyme, esterase D. Individuals with the retinoblastoma gene are heterozygous, having one normal and one mutant allele at 13q14. By studying tumors from individuals who were heterozygous for isoenzymes of esterase D or for chromosome 13 DNA probes that are polymorphic in the population, we have shown that retinoblastoma tumors have become homozygous for many genes in the vicinity of the retinoblastoma gene on the long arm of chromosome 13.

Three different mechanisms involving rearrangements of chromosome 13 (nondisjunction and duplication, simple loss, mitotic recombination) account for the change from heterozygosity to homozygosity in 7 of 10 RB tumors. The remaining three tumors do not show a shift to homozygosity but may have achieved the same result by point mutation, point deletion or gene conversion — changes which would not be detectable by the present chromosome 13 probes at variable distances from the RB locus.

We propose that the normal allele at 13q14 is a regulatory gene. The first mutation, the RB gene, heritable in bilateral cases, is loss or inactivation of one copy of this gene. Somatic loss of the other copy results in loss of regulatory function and uncontrolled proliferation. The other genetic changes, which we have observed in RB tumors, such as the unique isochromosome 6p and extra chromosome 1q, always are present by the time we obtain tumor cells, but may represent the inevitable progression once all normal copies of the 13q14 normal regulatory gene are missing. In tumors of other tissues, the chromosomal region that becomes homozygous may contain regulatory genes important for that tissue.

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*Project 399.

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LEUKEMIA PROGRAM AT THE ONTARIO CANCER INSTITUTE*

E. A. McCULLOCH** and J. E. CURTIS†, *Toronto, Ontario*

The close collaboration between clinicians and biologists in the Leukemia Program permits evaluation of the contribution of a number of factors to treatment outcome in acute myeloblastic leukemia (AML). These include disease-related attributes, such as percentage of blasts in a marrow, chemotherapeutic regimen and the sensitivity of blast cells in culture to drugs used in treatment. Biological features include: the growth characteristics of leukemic blasts in culture and the distribution of various immunologically-defined markers among freshly obtained blasts. Data from three different treatment protocols, each more aggressive than its predecessors, were evaluated in respect to factors contributing to variance. The findings were: Increasing aggression in chemotherapy did not increase significantly the success of remission induction or the length of survival. The sensitivities of blast cells to drugs were not significant contributors to outcome. In contrast, two attributes related to the nature of the disease in each patient were correlated both with successful remission induction and with prolonged survival. These were: The percentage of blasts in the marrow; and the capacity of blast progenitors to undergo self-renewal in culture.

Data were collected on the phenotypes of leukemic blasts as defined by a large panel of monoclonal or well-defined heteroantisera. Blast cells, apparently homogeneous on morphological criteria, were shown to be markedly heterogeneous in respect to the expression of immunologically-defined markers. The most striking feature of this heterogeneity was the identification of markers of more than one differentiation lineage on single AML blasts. This finding, termed "lineage infidelity", is not consistent with commonly held models of leukemia where blocked or frozen differentiation is postulated, often on the basis of phenotypic evidence suggesting "fidelity" to lineages.

The finding of lineage infidelity might be criticized both technically and theoretically. At a technical level, the specificity of the phenotyping reagents might be questioned; indeed, significant cross-reaction with cells outside the hemopoietic system has been observed. At a theoretical level, lack of a detailed description of pluripotent stem-cell phenotypes makes it possible that the presence of doubly-marked cells represents an expansion of a normal stem-cell population rather than abnormalities of gene expression reflected as bizarre cellular phenotypes.

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*Project 402.

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Two lines of evidence suggest that these objections lack force. Thousands of normal cells have been examined using the methods that were successful in detecting doubly-marked leukemic blasts; a doubly-marked cell has yet to be found in normal hemopoiesis, although the specificity of the immunological reagents within the blood-forming system was confirmed. Evidence for the biological significance of lineage infidelity was obtained from clinical studies. Among 39 AML patients, 15 were found to have doubly-marked blasts cells; of these only 2 achieved remission. In contrast, 17 of 24 patients without lineage infidelity responded to treatment; the difference is highly significant (p = .001). This is the most powerful association we have encountered between a laboratory-determined attribute and clinical outcome.

All of the data support the view that observations reflecting the biological nature of the disease are the most significant determinants of treatment outcome. The conclusion indicates the need for investigations of fundamental disease mechanisms. The significance of lineage infidelity as a predictor of poor prognosis gives a priority to studies directed towards the regulation of expression of lineage markers.

Model systems are now needed. One such is being developed from the observation that a line of T lymphoblasts (MOLT-3) continuously bearing T-lymphocyte markers, can be induced to express markers of other lineages following exposure to 5-azacytidine. Further, subclones can be isolated consisting of cells expressing both T-lymphocyte and granulopoietic markers simultaneously and for long periods of time. Characteristics of the induction of infidelity by 5-azacytidine and the properties of clones isolated from cells surviving the drug are now under investigation in the expectation that these will yield suitable models of lineage infidelity and abnormal gene expression.

SEARCH FOR PROGNOSTIC FACTORS IN CLINICALLY-STAGED PATIENTS WITH HODGKIN'S DISEASE*

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S. B. SUTCLIFFE†, T. CHUA‡ and R. S. BUSH††
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Treatment of clinical stage (CS) I and II Hodgkin's disease (HD) with local-regional irradiation (XRT) alone has been associated with a high relapse rate. The risk of relapse can be reduced by extended XRT fields and additional combination chemotherapy, without an improvement in overall survival. We have identified subgroups of CS I and II with an increased risk of relapse following XRT alone. From 790 HD patients treated at the Princess Margaret Hospital between 1968-77[1], we studied 252 patients ≥ 17 years with CS I and II (no laparotomy) who were treated with local (71), local-regional (130), or extended field (51) XRT alone. For this subgroup the significant factors predictive of relapse, identified by adjusted log-rank tests, were: histopathology ($p = 0.0007$); age ($p = 0.006$); stage ($p = 0.02$); and B-symptoms ($p = 0.04$).

Using these factors we grouped patients with a high, intermediate and low risk of relapse. The high-risk group included CS IA and IIA patients ≥50 with mixed cellularity (MC) or lymphocyte depletion (LD), those with B-symptoms and lymphocyte predominant (LP) and nodular sclerosis (NS), and those <50 and B-symptoms and MC/LD. Relapse occurred in 24/33 (0.727) patients in the high-risk group. The intermediate-risk group included CS IIA patients <50 with MC/LD, and ≥50 with LP/NS; relapse occurred in 19/42 (0.452) members of this group. All of the remaining patients were in the low-risk group with relapses in 49/171 (0.287). Six patients with unclassified HD are not included. Based on this analysis we have instituted the treatment policies shown in Table I for patients ≥17 with CS I and II (no laparotomy).

Patients with CS IA disease limited to the upper neck will be treated with radiation to the involved field, regardless of age or pathologic classification. Other patients in the low and intermediate risk groups would be treated with radiation to the upper mantle and upper abdomen. Patients with mediastinal adenopathy exceeding 10 cm in width have a high risk of relapse; these patients will be treated

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*Project 423.

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TABLE I

Treatment Policies for Supradiaphragmatic Clinical Stage I and II Hodgkin's Disease

Age	Pathology	IA		IIA	I and IIB
		Upper neck only	All others		
<50	LP/NS	Involved Field XRT	Exclude mediastinum ≥ 10 cm		
	MC/LD		Upper mantle and Upper abdomen XRT		MOPP x 3
≥50	LP/NS MC/LD		+ upper mantle + upper abdomen XRT		

MOPP to adequate control + 3500 cGy/20 to nodal areas + 1750 cGy/20 (corrected) to both lungs

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with MOPP chemotherapy until adequate tumor regression is achieved (usually three courses), and this will be followed by radiation, that is, 1750 cGy/20 (corrected) to both lungs. Patients in the high-risk group will be treated with three courses of MOPP, followed by radiation to the upper mantle and upper abdomen.

These treatment policies should reduce the risk of relapse. In addition, by standardizing the techniques of treatment, we should be able to identify sources of failure related to technical factors, define the first site of relapse, particularly with regard to control of upper abdominal disease by XRT alone, and improve the identification of patients with localized disease, who require chemotherapy as part of their initial management.

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CLASSIFICATION OF SURVIVAL CURVES[*]

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We are developing a methodology and a computer software package for the classification of survival curves into classes defined directly in clinical terms. Given a series of patients for which prognostic factors and survival data are recorded, the aim is to subdivide it into subpopulations, characterized by simple statements involving prognostic factors, such that their survival curves are clearly separated.

We have developed, in particular, a recursive partition (RP) algorithm based on pairwise comparisons of survival curves, and we have used it to analyze several data sets of clinical significance. The algorithm has been compared with regression analysis on a variety of data sets and found to have good statistical properties. More detailed comparisons are in progress.

An amalgamation algorithm (AA) has also been developed. In this algorithm we start from a group of distinct populations, each defined by a series of clinical statements, and successively merge pairs whose survival curves are not significantly different. Properties of the AA are being investigated.

Of the two algorithms, only the AA guaranties significantly distinct survival curves, for all pairwise comparisons of the final classes. Thus, at the moment, RP and AA are used in conjunction in order to obtain prognostic classification in the sense stated above.

In order to deal with more specific features of survival curves which occur in oncology, we have investigated the validity of the "proportional hazards" assumption and have developed new parametric and semi-parametric models based on broader assumptions[1,2].

Work in progress includes efforts to refine computational techniques, to improve efficiency in RP and the amalgamation algorithms, and to develop more general and flexible classification algorithms.

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[*] Project 426.

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EVALUATION OF NEW ULTRASOUND DIAGNOSTIC SYSTEMS TO DETECT AND CHARACTERIZE BREAST NEOPLASMS[*]

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The high incidence of breast cancer in North American women is of grave concern, therefore many diagnostic centres have been formed with the aim of reducing mortality through early detection. The special properties of high-resolution ultrasound scanners have the potential to complete or complement the traditional x-ray mammography examination, yet with no risk to the patient. The primary objective of this project was to develop such a high-resolution, effective ultrasound breast scanner, which can detect and characterize small (≥ 0.5 cm in diameter) abnormalities of the breast, and test such with a scanner in a clinical environment.

During the last year, a breast scanner based on an annular array transducer[1] has been replaced by a superior system developed by the Ultrasound Group at the Ontario Cancer Institute[2,3]. This novel cone/annular array hybrid design has demonstrated spatial resolution of approximately 0.5 mm in all directions. The expected improvement in image quality has been demonstrated and structures of the breast are clearly visualized. The modification of a commercial scanner to take this conical transducer has been completed successfully, and this system now has been installed at Women's College Hospital. Clinical evaluation of this scanner began October 1983 and the trial is showing increasing success in detecting malignancies and other abnormalities in the breast. We are continuing this study in which x-ray and ultrasound mammography will be compared in a random "blind" examination to test the accuracy of our ultrasound system.

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CLINICAL TRIALS IN BREAST CANCER[*]

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Four randomized controlled clinical trials are now in progress.
These are:

1. A randomized controlled trial of ovarian irradiation and prednisone, following operation and radiotherapy, was undertaken for carcinoma of the breast. This trial compared three forms of adjuvant therapy: ovarian irradiation and prednisone; ovarian irradiation alone; and no further treatment. There have been 756 patients enrolled and they now have been followed for at least eight years. In premenopausal women, aged 45 years or more, ovarian irradiation and prednisone significantly delayed recurrence, and prolonged survival. Further follow-up and analysis continue.
2. A randomized controlled trial of postoperative treatment of breast cancer is being conducted in premenopausal patients with histologically involved axillary nodes. This trial compares two treatment modalities: (a) combination chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF), and ovarian irradiation plus prednisone; and (b) CMF alone. The trial is designed to determine if chemotherapy and hormonal therapy are complementary. To date, 163 patients have been enrolled.
3. A randomized controlled trial of postoperative treatment of breast cancer is being conducted in postmenopausal patients with histologically involved axillary nodes. No currently available adjuvant therapy is known to benefit this group of patients and this trial examines the usefulness of tamoxifen as an adjuvant agent. To date, 373 patients have been enrolled. Overall the three-year, actuarial, relapse-free rates were 62% for patients receiving tamoxifen vs 49% for patients receiving no further treatment. As yet, there is no difference in overall survival between these two groups of patients. Estrogen receptor status was known in 195 patients and progesterone receptor status in 186. Improvement in disease-free

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[*] Project 446, including Projects 378 and 386.

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survival at present appears to be confined to the receptor-positive subgroup. These early results suggest that tamoxifen is useful in decreasing the recurrence rate in postmenopausal women with axillary-node-positive breast cancer following mastectomy because benefit appears to be confined to women with receptor-positive breast cancer.

4. In a Phase II trial, the value of tamoxifen in the treatment of metastatic breast cancer in premenopausal women is being studied. Of 53 evaluable patients, 4 have had complete responses (CR) and 10 have had partial responses (PR). Six patients have remained stable (ST) on treatment. The response rate (26% for CR + PR; 38% for CR + PR + ST) and the response duration (13+ months) seen in this study suggests that tamoxifen may achieve an effect comparable to that of ovarian ablation in premenopausal women with metastatic breast cancer. The study has also shown that steroid receptors generally were predictive of response to tamoxifen, and that tamoxifen response was highly predictive of response to subsequent ovarian ablation.

INVESTIGATION OF A STEM-CELL MODEL OF HUMAN TUMOR GROWTH*

R. N. BUICK**, A. CIAMPI† and J. E. TILL‡, *Toronto, Ontario*

We are investigating the possibility that human tumors are examples of cell-renewal systems and form "caricatures" of their normal tissue equivalents. The "tumor stem cell" population would be central to such cellular organization.

A number of models have been constructed as aids in our understanding of normal cell-renewal systems; these include the stochastic model and the clonal succession model. We have begun to apply similar concepts to human tumor-cell populations; a simple stem-cell model was used to clarify the biological principles underlying the use of tumor clonogenic assays as predictors of clinical outcome[1]. It is proposed to extend these studies in order to compare the usefulness of the stochastic and clonal succession models as aids in the understanding of human tumor-cell proliferation and the response of tumor-cell populations to therapeutic agents. The fundamental idea underlying the work is that it is the relationship between the rates of self-renewal, differentiation, transfer to quiescent states, and loss of tumor stem cells that is most influential in determining the growth properties of tumors. The objective of the project is to develop statistical methods for the estimation of these rates, based on analyses of experimental data derived from human tumor-cell populations.

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*Project 465.

**Senior Scientist, Ontario Cancer Institute, Toronto; and Associate Professor of Medical Biophysics, University of Toronto.

†Senior Scientist, OCI; and Assistant Professor of Medical Biophysics, U of T.

‡Senior Scientist, OCI; and Professor of Medical Biophysics, U of T.

IN VIVO ASSAYS USING THE CHICK EMBRYO TO STUDY HUMAN MALIGNANCY

V. LING**, *Toronto, Ontario* and
A. F. CHAMBERS†, *London, Ontario*

The growth and metastatic spread of tumors are complex processes involving interactions between tumor cells and normal tissues. To facilitate investigation of these interactions, it is desirable to exploit host systems in which aspects of these processes may be studied.

The chick embryo is an immune-deficient host able to support growth of a wide variety of transformed cells. Since growth of normal cells is not observed, this system appears to be generally useful for investigating malignant properties of different cells. We have developed a sensitive assay to quantitate rodent cells able to survive and grow in embryonic chick organs following i.v. injection[1]. We propose to use this assay as a model system for the study of certain aspects of the metastatic process. Recently we used DNA from murine and human melanoma cell lines (which grow well in chick embryo after i.v. injection) to transfect murine LTA cells (which do not grow in chick after i.v. injection). From the transfected LTA cells, we were able to isolate clones, which grow well in the chick after i.v. injection. Such clones were not observed in untransfected LTA cells or with LTA cells transfected with LTA DNA. These experiments clearly demonstrate the feasibility of using the chick embryo as a host system to study genes involved in growth-control alteration of the sort seen in malignant transformation.

REFERENCE

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*Project 467.

**Senior Scientist, Ontario Cancer Institute, Toronto; and Professor of Medical Biophysics, University of Toronto.

†Career Scientist, Ontario Cancer Foundation London Clinic; and Assistant Professor, University of Western Ontario, London.

University of Toronto

HORMONAL CONTROL OF PROSTATIC CANCER*

B. G. MOBBS**, *Toronto, Ontario*

Administration of the synthetic estrogen, diethylstilbestrol (DES) is a standard therapy for advanced prostatic cancer. Previously we observed that cancer tissue from patients undergoing this treatment sometimes has a high binding capacity for the synthetic androgen methyltrienolone (R1881).

The R3327 (Dunning) transplantable prostatic adenocarcinoma of the rat has many properties similar to those of human prostatic carcinoma, and has been widely used as a model for this disease. We have now examined the effect of DES treatment on the capacity of this experimental carcinoma to bind R1881. Both DES treatment and castration resulted in cellular redistribution of binding activity so that amounts of ^{3}H-R1881 bound by the nuclear fraction were insignificant in the treated animals. However, in DES-treated animals the total tissue-binding capacity was increased 2-3 fold over that in untreated animals.

The high-affinity binding of ^{3}H-R1881 in tumors from untreated and treated animals was characterized by Scatchard analysis, sucrose density gradient centrifugation, and steroid specificity studies. It was found that in untreated tumors, the binding was characteristic of androgen receptor protein (AR), while in DES-treated tumors it had characteristics of both AR and progesterone receptor (PgR). The presence of PgR was supported by preliminary binding studies using the synthetic progestin, R5020. Therefore it seems likely that estrogen treatment can induce the synthesis of PgR in R3327 prostatic carcinoma tissue. It is possible that part of the elevated binding capacity in human prostatic carcinoma after DES treatment may be due to induced PgR.

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*Project 251.

**Associate Professor of Surgery (Research), University of Toronto.

THE IRRADIATED LARYNX AND VOICE*

M. L. STOICHEFF**, *Toronto, Ontario* and
J. M. FREDRICKSON†, *St. Louis, Missouri*

At specific time intervals before and following radiotherapy, tape recordings were made of a standard passage read by 48 male patients with laryngeal cancer who received 5000 rads in 20 treatments over a period of four weeks at the Princess Margaret Hospital. Other data collected at these intervals included aerodynamic measures, information on smoking, alcohol intake, work environments, vocal usages and laryngeal examinations.

Relationship of Dysphonia Ratings to Other Variables

In a previous report, the voices of irradiated patients one year post-treatment were found to be significantly more dysphonic (deviated from normal voice) than controls matched for age. In this study, stepwise regression was used to order various life-style and clinical variables according to their ability to explain the variance of the dysphonia ratings. For both patients and controls, degree of dysphonia increased with age. Other variables associated with increased severity of dysphonia were scarring or paralysis of the vocal cords and employment in which talking occurred over machine noise or in fumes.

Speaking Fundamental Frequency Study

The fundamental frequency of the voice during reading was examined in patients one year post-treatment and in control subjects. No difference was found between the groups.

Study of Temporal Improvement in Voice

Perceptual ratings of the best voice achieved by each patient were made for 12 patients over six post-treatment periods: 0 months, 3-4 months, 5-6 months, 8-9 months, 1 year, 4-5 years. Results were variable with the highest frequency of best voices occurring in the 8-9 months period. Contrary to expectation, best vocal results were not most prominent in the later time periods.

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*Project 323.

**Professor of Speech Pathology, University of Toronto.

†Professor of Otolaryngology, Washington University, St. Louis, Missouri.

RESEARCH UNIT OF THE DIVISION OF EPIDEMIOLOGY AND STATISTICS OF THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION[*]

E. A. CLARKE[**], C. L. SOSKOLNE[†], N. KREIGER[‡] and
L. D. MARRETT[‡], *Toronto, Ontario*

The Research Unit operates within the Division of Community Health's Department of Preventive Medicine and Biostatistics at the University of Toronto. The Unit was established in 1978 to conduct analyses using the cancer data base of the Foundation, to assess the quality of the cancer data base, to co-operate with cancer researchers by providing epidemiological and statistical assistance, to conduct or support cancer research projects, and to provide information to the scientific community and the general public. The current report represents the first complete year during which the Research Unit has operated with its full complement of senior staff epidemiologists. Presented below are examples of some of the many projects, which have been undertaken.

Analysis of Data Base

The mortality data base is used to assess mortality rates for various areas within Ontario, for example, where the community is concerned about environmental carcinogens. At the 9th Clinical Cancer Research Conference provisional cancer incidence rates for Ontario were presented graphically for selected sites over the period 1964-1975. Potential years of life lost were shown for selected cancer sites. Incidence data were compared with mortality trends.

Data Quality

An examination of provisional site-specific incidence rates has revealed elevated incidence in the early years of the registry data collection (1964-1965). This likely is due to the inclusion of some cancer diagnoses made before 1964. We expect that this type of error will be reduced after further experience with specific projects for sites of interest.

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[*] Project 381.

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[†] Director, Research Unit, OCTRF; and Associate Professor in the Department of Preventive Medicine and Biostatistics, U of T.

[‡] Head of Statistics, OCTRF; and Associate Professor in the Department of Preventive Medicine and Biostatistics, U of T.

[‡] Epidemiologist, OCTRF; and Assistant Professor in the Departments of Preventive Medicine and Biostatistics, U of T, and of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton.

Co-operation with Researchers

The Research Unit continues its assistance to the clinical staff of the Windsor Clinic in its analysis of Stage II patients with breast cancer treated with a combination of radiotherapy and chemotherapy. Current analyses are examining recurrence, morbidity and survival in relation to estrogen receptor and progesterone status.

The cohort study of 4130 women followed for at least 20 years by Women's College Hospital has been completed.

The case-control study of female breast cancer, being conducted in Toronto in collaboration with the Boston School of Medicine's Drug Epidemiology Unit, is continuing; 200 cases of breast cancer and 400 neighbourhood controls have been inducted into the study. An additional 200 cases and 400 controls will be interviewed.

Continuing its collaboration with the International Agency for Research on Cancer, the Research Unit has provided the Ontario data for the International Radiation Study of cervical cancer patients, a study of low-dose irradiation and the occurrence of second primary malignancies. The Ontario portion comprises approximately 100 cases and 100 matched controls. The data are being coded, and will be analyzed over the next few months.

Research

The Unit's core group of four epidemiologists has special expertise in the following areas of etiologic research:

- female reproductive cancer
- occupational cancer
- case-control methodology
- precursor cancer conditions
- cancer trends in Ontario
- health consequences of cancer therapy
- cancer incidence generation for the Province of Ontario

Indices of reliability of cancer registration indicated that the reported incidence of cancer of the cervix in 1971 was too high. After a review of pathological confirmation and the deletion of those cases which were not cancer of the cervix the incidence rate fell to 15.1/100,000, compared to the original 20.5 reported by the registry.

Proposals have been prepared for studies of acquired immune deficiency syndrome (AIDS), based on a four-week feasibility study in Toronto — a community where AIDS is still rare and hence would be an ideal site for a study of potential precursor states of AIDS. If AIDS is a sexually transmitted disease caused by a virus, information gleaned from such research may yield important information about virally induced cancers and about the role of the immune system in the pathogenesis of cancer generally.

The Unit also made comparisons of worklife summary exposure measures in occupational case-control studies of disease etiology, followed up a cohort of benzidene-exposed workers, analyzed risk factors for lower urinary tract cancers from case-control data, analyzed risk factors for endometrial hyperplasia from case-control data, and examined the incidence and mortality trends of cancers of special interest, particularly Hodgkin's disease, testicular cancer, ovarian and endometrial cancer.

With the advent of Ontario cancer incidence data, further examinations will be carried out to check the completeness and accuracy of the registry.

CONSTRUCTION AND TESTING OF CODED-APERTURE COLLIMATION SYSTEMS FOR GAMMA-RAY CAMERAS*

M. L. G. JOY**, *Toronto, Ontario*

The purpose of this research is to construct and test a novel, relatively inexpensive, tomographic imaging system for use in nuclear medicine. The system being investigated is called Fourier multiaperture emission tomography (FMET)[1]. Physically it is a collimator, which is mounted on a gamma camera like a regular collimator. The FMET collimator allows the positioning of any one of a number (now 32) of coded-aperture plates in front of the camera. The coded images produced by these plates are processed digitally to form a series of tomographic "slices" in planes parallel to the camera. The thickness of these slices increases with depth but is about 1.6 cm at 10 cm from the plate. The resolution in the plane is about 8 mm. Currently, 10 to 20 minutes is required for the acquisition of the coded images. Processing time has been reduced to 45 sec per slice.

With the exception of the publication of the final results this project is complete. The noise performance of the FMET system has been measured and compared with theory[2]. The results of this comparison have led us to conclude that this theory accurately predicts the statistical performance of FMET. In addition to this work, a possible modification to this method has been tested, which leads to a 35% improvement in the deviation of the quantum noise.

Our conclusion with respect to the potential usefulness of this technique is that, at present the potential benefits of its tomographic capability are out-weighted by the high quantum noise observed in practice. The root of the problem is the high counting rates, which are encountered due to the largely open FMET apertures. The technique therefore is limited to situations in which small amounts (200 μCi) of activity are used and the noise problem, consequently, is severe.

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2. Joy MLG, Renaud L, Gilday D: Fourier multiaperture emission tomography: Quantum noise calculations. *Optical Engineering* 1981; **20** (5): 736.

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*Project 413.

**Associate Professor, Institute of Biomedical Engineering and Department of Electrical Engineering, University of Toronto.

EPIDEMIOLOGY OF CERVICAL DYSPLASIA*

E. A. CLARKE** and G. LICKRISH†, *Toronto, Ontario*

This the final report of a case-control study in which information on risk factors associated with cervical dysplasia, and detailed smoking histories, were collected from 250 cases and 500 controls matched on age and neighbourhood. Cases were women between the ages of 20 and 59 years with histologically proven cervical dysplasia, who were residents of Toronto and Mississauga, Ontario.

The statistically significant independent risk factors in the development of cervical dysplasia were the number of sexual partners, age at first intercourse and smoking status. Simultaneous adjustment for the significant risk factors showed that: Current smokers have approximately twice the risk of developing cervical dysplasia compared with those who never smoked, and the risk increased with increasing quantity of cigarettes smoked. Women with multiple sexual partners have a greater risk than women with only one; and women who had intercourse before the age of 18 have an almost twofold risk of developing cervical dysplasia, when compared with those who had first intercourse later. A crude increased risk of both the use and duration of oral contraceptives disappeared after adjustment for the above three risk factors. Smoking, by depressing the immune mechanism, might permit a sexually transmitted agent to result in abnormal cellular development leading to the onset of cervical dysplasia.

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*Project 414. (Final Report)

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EVALUATION OF ELECTROMECHANICAL LARYNX*

V. S. DAYAL** and M. L. G. JOY†, *Toronto, Ontario*

Laryngeal cancer accounts for 1.8% of carcinoma seen every year in Ontario. The conventional treatment for these is operation, radiation or a combination of both. A crude estimate of the number of laryngectomies performed each year, based on data from the Ontario Cancer Treatment and Research Foundation and the American Cancer Society, is approximately 284 in Ontario and 8000 in North America. The two major handicaps following laryngectomy are an often poor voice, esophageal speech, and a permanent tracheostoma. Several devices have been built and surgical procedures developed to improve the quality of speech, however, none has been very successful. Fistula technique, creation of a fistula between trachea and pharynx, gives a reasonable speech but has been associated with stenosis of fistula and aspiration.

The applicants have built an endotracheal artificial larynx, which, when placed in a surgically created, large tracheopharyngeal fistula following laryngectomy in experimental animals, has prevented aspiration and has provided an adequate airway.

During the past year of this grant support, further experiments have been carried out to gain a better understanding of the triggering mechanism of this device. A new, simpler and stable circuit has been developed for long-term patient use. A number of these devices were made, and this has been on clinical trial in one patient.

A series of five articles have been published as a supplement in the *Annals of Otology, Rhinology and Laryngology*.

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*Project 451.

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Women's College Hospital, Toronto

COHORT STUDY OF FACTORS ASSOCIATED WITH THE DEVELOPMENT OF BREAST CANCER

K. I. PRITCHARD[**], M. WYNNE-JONES[†], G. McKEOWN-EYSSEN[‡]
and C. L. SOSKOLNE[‡‡], *Toronto, Ontario*

Initially this project, which was started at Women's College Hospital in 1945, by Dr. Helen Bell Milburn, was designed to determine the relationship between breast changes at menstruation, pregnancy, lactation and menopause, and the subsequent development of breast cancer. Between 1945 and 1972, 4136 volunteers were enrolled in the study, including 3223 students from successive nursing classes in Toronto hospitals. Detailed history and physical examinations were recorded on an initial questionnaire at the time of enrolment and the cohort was followed at three-year intervals.

By 1978, it was possible to contact 77% (79% of the student-nurse subset) to obtain information. An analysis, based on this updated information and on the original questionnaire was done by Dr. E. Aileen Clarke and Ms Terry Germanson and has been submitted for publication. In 1979, a further questionnaire was mailed to the entire cohort and 74% (78% of the student-nurse subset) were contacted for further information on a number of variables. Information from the original interviews and examinations of the women in the cohort, and the information from the interval examinations and from the most recent questionnaire has been computerized.

In the student-nurse subset, 46 women had developed breast cancer under the age of 50. A cohort analysis on the first questionnaire variables only showed that

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[*] Projects 11 and 433.

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family history of ovarian cancer, breast changes during the menstrual period and irregular periods were strongly, statistically associated with the development of breast cancer. A case control analysis was also done: three controls were selected for each of the 46 patients who developed breast cancer under the age of 50; they were matched by age at study entry, date of study entry, age at menarche, family history of breast cancer, and length of follow-up. Once again, an analysis using first questionnaire variables confirmed the significance of breast changes during the period and irregular periods as risk factors associated with the development of breast cancer. Then a case control analysis was attempted on the first and second questionnaire variables combined. However, only 10 cases had complete information on all the variables we wished to test and a first questionnaire analysis on these ten sets showed that they were not representative of the overall group. Thus this approach was not pursued. A paper is being prepared for publication describing this analysis.

Ontario Cancer Foundation Windsor Clinic

CLINICAL INVESTIGATION

Dr. J. H. Maus, Director of the Windsor Clinic, reports on the following clinical research investigation:

ADVANCED BREAST CANCER

The Windsor Clinic is conducting a pilot study to test the efficacy of mitoxantrone (DHAD) and cyclophosphamide as first-line treatment in advanced breast carcinoma (Stage IV). The objective is to develop a chemotherapy as effective as Adriamycin and cyclophosphamide yet without the latter's cardiac and general toxicity. Patient acceptance has been satisfactory and early results show clinical efficacy in soft tissue, liver and bony metastases. Long-term safety and survival advantages have yet to be determined.

EPIDEMIOLOGY AND STATISTICS

CANCER MORTALITY, INCIDENCE AND TREATMENT IN ONTARIO

E. A. CLARKE, M.B., B.S.*, N. KREIGER, M.P.H., Ph.D.**
L. D. MARRETT, Ph.D.** and C. L. SOSKOLNE, Ph.D.**
Toronto, Ontario

The Division of Epidemiology and Statistics is responsible for one of the mandates of the Foundation under The Cancer Act, namely the adequate reporting of cases and the recording and compilation of data. Towards this objective, the Foundation has maintained and improved a uniform case recording system adopted by the regional treatment centres in 1947 and incorporating the Ontario Cancer Institute and the Princess Margaret Hospital since it was founded in 1957. These data, from both the regional treatment centres and the Princess Margaret Hospital, are in machine-readable form from 1960 onwards. In addition to these records, the computerized cancer data base of the Foundation contains individual records on residents of Ontario who died from cancer since 1950; tabulations by sex, 5-year age groups and site of cancer deaths from 1931 to 1981; individual records of patients diagnosed as having cancer in the province between 1964 and 1975; individual records of hospital discharges on patients with cancer from 1964 to 1982; pathology reports on specimens with cancer from 1972 to 1982. The total volume of records, in excess of three million, provides the Division with a unique opportunity for descriptive cancer epidemiology and allows the Division to assist other cancer researchers in the investigation of possible carcinogenic effects of exposure to occupational and environmental agents.

Most of the staff of the Division is located in the Head Office of the Foundation at 7 Overlea Boulevard but the Research Unit of the Division is located in the Department of Preventive Medicine and Biostatistics at the Faculty of Medicine of the University of Toronto. Drs. E. A. Clarke, N. Kreiger, L.D. Marrett and C. L. Soskolne all have cross-appointments in the Department of Preventive Medicine and Biostatistics. This arrangement allows the staff of the Division to interact with other members of the epidemiological community as well as with medical and oncological colleagues.

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CANCER MORTALITY

Computerized data on deaths due to all causes in Ontario residents in 1982 have been provided by the Office of the Registrar General of Ontario. These data are summarized in Tables I and II, where one can assess the relative impact of cancer as a cause of death. In 1982, 34,825 male and 29,254 female (and 1 infant of unrecorded sex) residents of Ontario died.

Table I shows that, for males, only a small proportion of deaths in the younger age groups are due to malignant neoplasms. The majority of deaths in those 15-34 years old are due to trauma. In the three older age groups, however, as a cause of death, malignant neoplasms rank second after diseases of the circulatory system, and account for more than 8,300 deaths.

In contrast to males, females are somewhat less likely to die of trauma and more likely to die of malignant neoplasms in the age group 15-34 years (Table II). In addition, not only is cancer the leading cause of death in women 15-34 years old, but fully 50% of deaths in this group are due to malignant neoplasms. The cause-of-death distributions for females in the two oldest age-groups are similar to those for males: malignant neoplasms rank second, after diseases of the circulatory system.

As has been true for nearly three decades, malignant neoplasms of the trachea, bronchus, and lung rank first among cancers as a cause of death in males, over all ages and within each 5-year age group from 35 years and older (Table III, Fig. 1). In those dying before age 35, leukemia, among the cancer causes of death, is the first-ranked. Second- and third-ranked male cancer causes of death in all age groups combined, are cancer of the intestine (except rectum) and cancer of the prostate; all of the digestive tract tumors shown rank among the top 10 for males.

For at least 50 years, the most frequent cause of cancer death in females has been cancer of the breast (Table IV, Fig. 1). Second-ranked is cancer of the trachea, bronchus, and lung, accounting for nearly 1,000 deaths in Ontario women. As for males, the digestive sites shown all rank in the top 10 cancer causes of death, with the exception of cancer of the esophagus. Nearly 800 deaths are due to malignant neoplasms of the major female reproductive organs (cervix uteri, other uterus, and ovary); cancer of the ovary alone accounts for most of these and ranks fourth as a cancer cause of death.

Table V shows the distribution of 1982 cancer deaths by site, and the percentage of deaths autopsied at each site. The autopsy rate is low compared with other (e.g. Scandinavian) countries, about 13%, although leukemia and lymphoma deaths are somewhat more likely to be autopsied.

CANCER INCIDENCE

In late 1983, as part of the Ontario Cancer Treatment and Research Foundation's 40th anniversary celebrations, the Ontario Cancer Registry presented provisional incidence data for the province, for the years 1964 to 1975. The data are provisional in that they have not yet been linked with the file of 1972-1975 cancer deaths. Although it is unlikely that this final linkage will significantly alter cancer incidence rates, it is possible that the frequencies by site will change.

TABLE I

Frequency (No.) and Per Cent (%) Distributions of Major Causes of Death in Males Within Age Groups, Ontario, 1982[1]

CAUSE OF DEATH	ICD9[2] NUMBER	AGE AT DEATH (YEARS)									
		0-14		15-34		35-54		55-74		75+	
		No.	%	No.	%	No.	%	No.	%	No.	%
Malignant neoplasms	140-208	58	6	142	8	909	25	4,751	31	2,511	19
Diseases of the nervous system	320-389	31	3	47	3	63	2	187	1	170	1
Diseases of the circulatory system	390-459	18	2	105	6	1,412	38	7,368	48	7,221	56
Diseases of the respiratory system	460-519	25	3	35	2	90	2	933	6	1,448	11
Diseases of the digestive system	520-579	13	1	21	1	249	7	679	4	393	3
Congenital anomalies	740-759	193	21	21	1	20	1	25	0	5	0
Injury and poisoning	800-999	164	17	1,264	73	666	18	596	4	314	3
Other	Other	437	47	91	6	264	7	938	6	944	7
ALL CAUSES	All	939	100	1,726	100	3,673	100	15,477	100	13,006	100

[1] Omitted are four males of unrecorded age and one infant of unrecorded sex.

[2] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

TABLE II

Frequency (No.) and Per Cent (%) Distributions of Major Causes of Death in Females Within Age Groups, Ontario, 1982[1]

CAUSE OF DEATH	ICD9[2] NUMBER	AGE AT DEATH (YEARS)									
		0-14		15-34		35-54		55-74		75+	
		No.	%	No.	%	No.	%	No.	%	No.	%
Malignant neoplasms	140-208	39	6	141	22	1,097	50	3,435	37	2,376	14
Diseases of the nervous system	320-389	23	4	23	4	58	3	157	2	180	1
Diseases of the circulatory system	390-459	20	3	54	8	419	19	3,786	40	10,448	64
Diseases of the respiratory system	460-519	22	4	21	3	77	4	481	5	1,040	6
Diseases of the digestive system	520-579	7	1	16	2	110	5	402	4	604	4
Congenital anomalies	740-759	148	24	15	2	8	0	25	0	9	0
Injury and poisoning	800-999	78	13	319	49	280	13	336	4	412	3
Other	Other	282	45	67	10	125	6	718	8	1,393	8
ALL CAUSES	All	619	100	656	100	2,174	100	9,340	100	16,462	100

[1] Omitted are three females of unrecorded age and one infant of unrecorded sex.

[2] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

TABLE III

Number of Deaths due to Malignant Neoplasms in Males, by Site of Disease and Age at Death, Ontario, 1982

SITE OF DISEASE	ICD9[1] NUMBER	AGE AT DEATH (YEARS)																	RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	All Ages	
Lip and oral cavity	140-145	—	—	1	—	1	—	—	—	6	7	7	15	20	12	19	32	120	15
Pharynx	146-148	—	—	—	—	—	1	1	—	1	7	6	8	12	11	8	12	67	
Esophagus	150	—	—	—	—	—	—	—	—	2	6	5	30	40	36	30	68	217	10
Stomach	151	—	—	—	—	—	1	1	4	6	11	33	41	57	60	68	156	438	5
Intestine, except rectum	152,153	—	—	—	—	2	—	5	6	9	19	33	54	112	111	124	253	728	2
Rectum and anus	154	—	—	—	—	—	1	—	2	2	8	12	26	38	45	57	93	284	8
Pancreas	157	—	—	—	1	1	1	1	4	5	8	26	48	60	79	88	128	450	4
Nasal cavities, middle ear and accessory sinuses	160	—	—	—	1	—	1	—	—	—	1	1	3	—	1	1	4	13	
Larynx	161	—	—	—	—	—	—	—	—	1	3	12	18	21	16	23	30	124	13.5
Trachea, bronchus and lung	162	—	—	—	—	—	—	2	17	41	59	169	310	414	516	549	644	2721	1
Bone	170	—	—	2	4	1	1	1	1	—	2	3	—	1	3	1	1	21	
Connective tissue	171	—	1	1	1	2	1	2	2	4	4	1	3	3	1	4	9	39	
Malignant melanoma	172	—	—	—	—	1	2	2	7	8	6	9	21	9	11	8	15	99	
Breast	175	—	—	—	—	—	—	—	—	—	—	—	1	—	2	1	4	8	
Prostate	185	—	—	—	—	—	—	—	1	—	2	9	27	35	108	134	401	717	3
Testis	186	—	—	—	1	4	5	1	1	1	1	1	2	—	3	1	—	21	
Bladder	188	—	—	—	—	—	—	—	—	2	2	12	14	26	49	58	135	298	7
Kidney and ureter	189.0-189.2	1	—	—	—	—	1	—	2	5	6	18	25	28	24	21	48	179	11
Brain and other nervous system	191,192	3	3	4	4	4	3	11	4	8	15	27	44	37	34	26	22	249	9
Thyroid gland	193	—	—	—	—	—	—	—	—	—	—	1	1	1	5	3	2	13	
Lymphosarcoma and reticulosarcoma	200	—	—	1	2	3	4	—	2	2	3	5	10	7	12	13	15	79	
Hodgkin's disease	201	—	—	—	2	1	4	2	3	2	2	3	3	4	2	9	11	48	
Other lymphomas	202	1	—	4	—	1	4	—	4	2	5	7	24	21	22	17	48	160	12
Multiple myeloma	203	—	—	—	—	—	—	—	—	1	3	5	11	17	25	17	45	124	13.5
Leukemia	204-208	5	15	6	6	12	4	8	10	11	7	26	16	33	42	60	110	371	6
Other and non-specific	Residual	5	5	—	1	5	5	5	9	18	21	53	84	81	136	116	213	757	
TOTAL	140-208[3]	15	24	19	23	38	39	42	79	137	208	484	839	1077	1366	1456	2499	8345	

[1] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.
[2] Rank order for sites with more than 100 deaths.
[3] Omitted are 26 deaths due to non-melanotic cancer of the skin (ICD9 number 173).

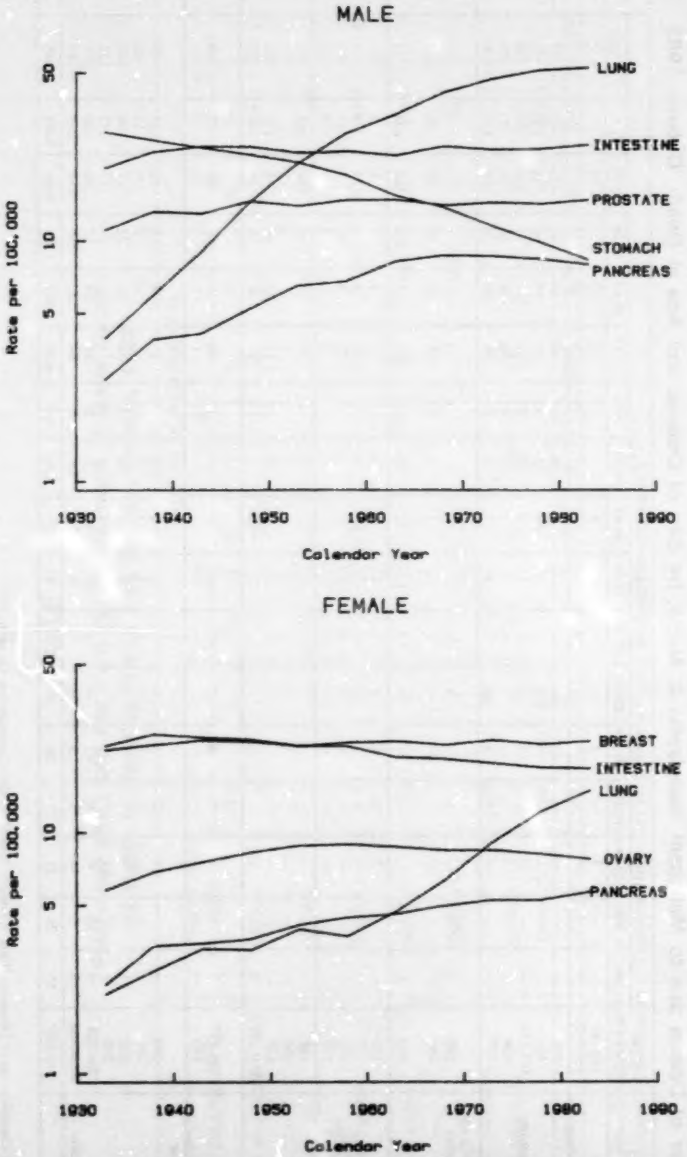

Fig. 1 Age-adjusted mortality rates for selected cancer sites, by sex, Ontario, 1931-1981. (Age adjustment is to the world population.)

TABLE IV

Number of Deaths due to Malignant Neoplasms in Females, by Site of Disease and Age at Death, Ontario, 1982

SITE OF DISEASE	ICD9[1] NUMBER	AGE AT DEATH (YEARS)																	RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	All Ages	
Lip and oral cavity	140-145	—	—	—	—	—	—	—	2	4	1	4	6	5	10	6	26	64	
Pharynx	146-148	—	—	—	—	—	—	1	—	3	—	1	4	6	4	5	7	31	
Esophagus	150	—	—	—	—	—	—	—	1	—	2	4	5	6	14	11	40	83	
Stomach	151	—	—	—	—	—	3	4	3	4	13	10	19	29	25	42	150	302	6
Intestine, except rectum	152,153	—	—	—	—	2	—	6	7	11	20	48	56	80	88	116	373	807	3
Rectum and anus	154	—	—	—	—	—	—	1	4	2	3	8	22	20	24	30	117	231[4]	8
Pancreas	157	—	—	—	—	—	—	—	—	3	3	27	24	36	51	69	146	359	5
Nasal cavities, middle ear and accessory sinuses	160	—	—	—	—	—	—	—	—	—	1	—	1	1	—	1	1	5	
Larynx	161	—	—	—	—	—	—	—	—	1	—	2	4	1	5	3	8	24	
Trachea, bronchus and lung	162	—	—	—	1	—	—	5	11	29	48	73	139	160	155	138	194	953	2
Bone	170	—	—	3	1	1	—	2	1	1	—	1	2	1	1	—	2	16	
Connective tissue	171	—	1	—	1	2	1	5	1	—	2	6	2	4	2	2	3	32	
Malignant melanoma	172	—	—	—	—	1	2	4	4	1	7	8	8	4	5	3	16	63	
Breast	174	—	—	—	—	—	2	22	44	62	79	171	174	178	199	156	348	1435	1
Cervix uteri	180	—	—	—	—	—	6	6	8	16	10	14	23	25	22	28	37	195	9
Other uterus	179,181,182	—	—	—	—	—	—	2	1	1	3	7	12	28	38	27	58	177	11
Ovary	183.0	1	—	—	1	2	3	3	7	11	25	28	62	58	65	55	103	424	4
Bladder	188	—	—	—	—	—	—	—	—	—	4	—	5	8	9	20	68	114	14
Kidney and ureter	189.0-189.2	—	—	—	2	—	—	2	1	3	6	4	9	14	19	12	33	105	15
Brain and other nervous system	191,192	6	4	3	1	5	5	3	4	11	12	16	27	20	13	20	31	181	10
Thyroid gland	193	—	—	—	—	1	—	—	—	—	—	3	—	2	4	3	14	27	
Lymphosarcoma and reticulosarcoma	200	—	—	—	—	—	—	1	1	4	3	3	5	9	5	12	17	60	
Hodgkin's disease	201	—	—	—	—	—	—	2	2	1	1	4	2	3	4	2	12	33	
Other lymphomas	202	—	1	1	—	3	—	—	3	5	5	14	13	16	18	27	53	159	12
Multiple myeloma	203	—	—	—	—	—	—	1	—	1	2	9	9	10	16	31	54	133	13
Leukemia	204-208	5	4	3	2	2	4	7	7	7	6	12	12	17	25	39	97	249	7
Other and non-specific	Residual	3	3	1	3	—	3	4	10	15	19	27	62	87	90	123	358	808	
TOTAL	140-208[3]	15	13	11	12	19	29	81	122	196	275	504	707	828	911	981	2366	7070	

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[1] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.
[2] Rank order for sites with more than 100 deaths.
[3] Omitted are 18 deaths due to non-melanotic cancer of the skin (ICD9 number 173).
[4] Omitted is one female of unrecorded age.

TABLE V

Number of Deaths Due to Malignant Neoplasms and Per Cent Autopsied, by Site of Disease, Ontario, 1982

SITE OF DISEASE	ICD9[1] NUMBER	NUMBER OF DEATHS	PER CENT AUTOPSIED
Lip and oral cavity	140-145	184	7.6
Pharynx	146-148	98	11.2
Esophagus	150	300	15.0
Stomach	151	740	9.7
Intestine, except rectum	152,153	1,535	11.1
Rectum and anus	154	516	7.8
Pancreas	157	809	15.0
Nasal cavities, middle ear and accessory sinuses	160	18	16.7
Larynx	161	148	10.8
Trachea, bronchus and lung	162	3,674	13.3
Bone	170	37	13.5
Connective tissue	171	71	12.7
Malignant melanoma	172	162	17.3
Breast	174,175	1,443	9.7
Cervix uteri	180	195	10.8
Other uterus	179,181,182	177	12.4
Ovary	183.0	424	13.2
Prostate	185	717	7.7
Testis	186	21	19.1
Bladder	188	412	9.7
Kidney and ureter	189.0-189.2	284	18.0
Brain and other nervous system	191,192	430	15.8
Thyroid gland	193	40	20.0
Lymphosarcoma and reticulosarcoma	200	139	21.6
Hodgkin's disease	201	81	33.3
Other lymphomas	202	319	24.8
Multiple myeloma	203	257	12.1
Leukemia	204-208	620	23.2
Other and non-specific	Residual	1,565	12.3
TOTAL	140-208[2]	15,416	12.9

[1] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

[2] Omitted are 44 deaths due to non-melanotic cancer of the skin (ICD9 number 173).

The Registry employs a passive reporting system whereby information on cancer, which is collected routinely for other purposes, is forwarded to the Registry. Records referring to the same individual are brought together by a computer linkage system, generously donated by Statistics Canada and modified by the OCTRF Division of Information Systems, with the assistance of Dr. G. R. Howe of the National Cancer Institute of Canada Epidemiology Unit.

The Registry receives more than 150,000 records each year: 100,000 hospital discharge reports with a diagnosis of cancer; 30,000 pathology reports with a mention of cancer; 18,000 reports on patients treated at the Foundation treatment centres and the Princess Margaret Hospital; and 16,000 death certificate reports on Ontario residents whose deaths were due to cancer. With the exception of pathology reports, these records are received on computer-readable magnetic tape. The pathology reports are coded and entered into the computer system at the Registry. Once the data from the different sources are entered into the Registry, a sequence of record linkages is performed to generate incidence data (Fig. 2).

The Registry anticipates that the generation of provisional incidence data to cover the period 1964-1982 will be nearing completion by the end of 1984.

Since 1978, the hospital discharge information provided to the Registry contains information about surgical procedures, chemotherapy, and length of stay; these additional pieces of information will make the Registry an ever more valuable resource in future years.

Table VI and VII display the estimated annual numbers of new cases of cancer among males and females, respectively, according to age at diagnosis and cancer site for the most recent 3 years of data, namely 1973-1975. The frequencies shown are averages of the 1973, 1974 and 1975 numbers. These tables are identical in format to those described in the CANCER MORTALITY section above (Tables III and IV), so that comparisons between incidence and mortality can be made for a given site, or for all sites combined (Fig. 3). It should be noted, however, that the incidence and mortality tables differ slightly with respect to site definitions, since mortality data were coded according to the Ninth Revision of the International Classification of Diseases (ICD), in use in 1982, while incidence data were coded to the Eighth Revision of the ICD, which was being used in 1973-1975. The reader should be aware that these two revisions do differ somewhat, so that the site definitions in the mortality tables are not always strictly comparable with their incidence counterparts. For the sites shown, however, any differences would have a very small impact on the frequencies displayed.

As for mortality in 1982, incident malignant neoplasms of the trachea, bronchus, and lung comprised the leading cancer in males in 1973-1975 (Table VI, Fig. 4), accounting for 20% of new cancer cases. That ranking second, cancer of the prostate, accounted for 14% of new male cancers, followed by those of the intestine (except rectum) (9%) and bladder (8%). These four sites alone accounted for more than one-half of all new male cancers in Ontario.

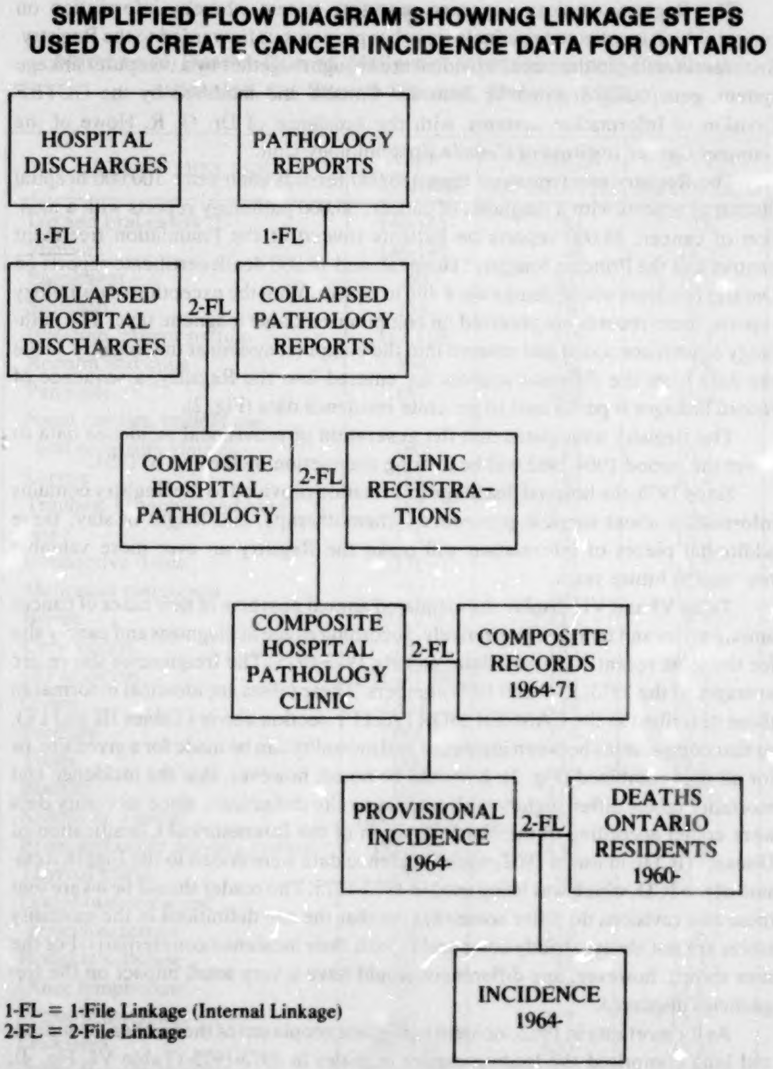
SIMPLIFIED FLOW DIAGRAM SHOWING LINKAGE STEPS USED TO CREATE CANCER INCIDENCE DATA FOR ONTARIO
HOSPITAL DISCHARGES
PATHOLOGY REPORTS
1-FL
1-FL
COLLAPSED HOSPITAL DISCHARGES
2-FL
COLLAPSED PATHOLOGY REPORTS
COMPOSITE HOSPITAL PATHOLOGY
2-FL
CLINIC REGISTRA-TIONS
COMPOSITE HOSPITAL PATHOLOGY CLINIC
2-FL
COMPOSITE RECORDS 1964-71
PROVISIONAL INCIDENCE 1964-
2-FL
DEATHS ONTARIO RESIDENTS 1960-
INCIDENCE 1964-
1-FL = 1-File Linkage (Internal Linkage)
2-FL = 2-File Linkage

Fig. 2 Flow diagram showing the steps of record linkage necessary to generate cancer incidence data for Ontario.

TABLE VI

Average Annual Number of New Cases of Malignant Neoplasms in Males, by Site of Disease and Age at Diagnosis, Ontario, 1973-1975

SITE OF DISEASE	ICD8[1] NUMBER	AGE AT DIAGNOSIS (YEARS)																		RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	Age Unknown	All Ages	
Lip and oral cavity	140-145	—	1	1	1	1	4	3	13	21	36	50	56	71	70	58	102	5	493	7
Pharynx	146-148	1	—	—	1	1	1	1	5	9	13	21	20	22	24	21	19	—	159	
Esophagus	150	—	—	—	—	—	—	—	1	4	12	17	27	32	35	27	41	1	197	15
Stomach	151	1	—	—	—	—	2	2	7	18	31	43	55	84	93	102	165	5	608	6
Intestine, except rectum	152,153	1	1	—	1	3	5	10	13	26	46	80	110	166	180	184	309	7	1142	3
Rectum and anus	154	—	—	—	1	2	1	4	8	15	33	60	70	95	106	97	167	7	666	5
Pancreas	157	—	—	—	—	1	2	2	4	7	12	25	38	49	49	59	80	2	330	9
Nasal cavities, middle ear and accessory sinuses	160	—	—	1	—	1	—	1	2	2	8	6	9	8	8	8	13	—	67	
Larynx	161	—	—	—	—	—	1	1	1	14	21	37	40	48	37	32	33	1	266	13
Trachea, bronchus and lung	162	2	—	2	1	1	4	6	17	53	116	219	301	437	441	399	407	11	2417	1
Bone	170	1	1	6	11	9	3	2	3	3	2	5	4	7	7	5	11	1	81	
Connective tissue	171	2	2	3	2	2	4	4	3	5	8	9	6	4	7	9	11	2	83	
Malignant melanoma	172	1	1	1	3	10	12	18	14	17	18	24	22	18	16	10	23	3	211	14
Breast	174	—	—	—	—	—	—	1	2	4	6	9	8	10	11	11	19	—	81	
Prostate	185	3	—	—	—	—	1	—	1	2	9	34	85	178	269	325	728	14	1649	2
Testis	186	2	—	1	7	18	27	22	15	15	11	6	4	4	2	1	2	—	137	
Bladder	188	1	1	—	1	3	6	7	13	22	43	60	88	120	145	148	249	12	919	4
Kidney and ureter	189.0-189.2	6	1	2	1	1	1	4	6	12	28	30	28	42	38	28	45	2	275	10.5
Brain and other nervous system	191,192	16	12	13	6	9	7	9	13	18	24	29	29	26	23	18	15	2	269	12
Thyroid gland	193	—	—	—	2	4	4	4	3	4	5	6	4	3	5	4	4	1	53	
Lymphosarcoma and reticulosarcoma	200	5	2	5	5	7	5	9	8	16	18	22	30	35	34	28	45	1	275	10.5
Hodgkin's disease	201	1	2	6	13	19	16	12	8	12	9	9	7	8	7	6	8	1	144	
Other lymphomas	202	2	2	2	3	4	4	5	5	7	10	12	12	14	13	11	17	3	126	
Multiple myeloma	203	1	—	1	1	—	—	1	1	5	7	8	12	17	20	27	35	2	138	
Leukemia	204-207	36	16	18	17	12	13	13	11	12	20	30	29	42	51	51	90	2	463	8
Other and non-specific	Residual	12	2	3	4	6	11	11	13	26	44	80	73	103	120	113	225	16	862	
TOTAL	140-207	94	44	65	81	114	134	152	190	349	590	931	1167	1643	1811	1782	2863	101	12111	

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[1] ICD8 International Classification of Diseases, Eighth Revision, World Health Organization, Geneva, 1967.
[2] Rank order for sites with more than 200 cases.

TABLE VII

Average Annual Number of New Cases of Malignant Neoplasms in Females, by Site of Disease and Age at Diagnosis, Ontario, 1973-1975

SITE OF DISEASE	ICD8[1] NUMBER	AGE AT DIAGNOSIS (YEARS)																		RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	Age Unknown	All Ages	
Lip and oral cavity	140-145	—	—	1	—	2	4	4	5	8	14	16	20	23	24	20	44	1	186	15
Pharynx	146-148	—	—	—	—	1	—	—	—	1	7	6	10	8	10	5	7	—	55	
Esophagus	150	1	—	—	—	—	—	1	—	2	3	6	6	8	11	18	32	1	89	
Stomach	151	—	—	—	—	1	—	3	8	5	16	22	25	34	45	60	147	1	367	8
Intestine, except rectum	152,153	2	1	—	2	3	4	11	20	27	48	94	117	159	195	217	482	7	1389	3
Rectum and anus	154	—	—	—	—	2	2	3	6	16	29	44	53	58	72	73	166	6	530	7
Pancreas	157	—	—	—	—	—	—	1	2	6	11	12	24	33	38	41	95	2	265	11
Nasal cavities, middle ear and accessory sinuses	160	1	—	—	—	—	1	1	1	2	5	4	5	7	3	7	13	1	51	
Larynx	161	—	—	—	1	—	1	—	2	3	3	7	6	7	5	5	6	1	47	
Trachea, bronchus and lung	162	1	—	—	1	2	3	5	11	29	49	71	85	96	79	74	105	6	617	5
Bone	170	—	2	7	7	4	3	2	3	1	3	2	4	4	5	6	10	1	64	
Connective tissue	171	3	1	1	4	2	4	3	2	5	6	4	5	4	9	6	15	1	75	
Malignant melanoma	172	—	1	1	8	13	20	19	19	17	29	29	21	15	18	13	33	4	260	13
Breast	174	2	—	1	2	6	29	69	143	277	430	448	385	403	357	301	599	18	3470	1
Cervix uteri	180	1	—	—	9	96	314	307	254	224	183	144	118	93	65	49	66	19	1942	2
Other uterus	181,182	—	—	1	2	4	7	11	18	33	74	163	197	168	110	91	114	5	998	4
Ovary	183.0	—	1	2	4	10	10	13	20	34	54	66	68	73	63	47	65	3	533	6
Bladder	188	—	—	—	1	—	2	2	5	8	17	24	24	42	39	52	127	3	346	9
Kidney and ureter	189.0-189.2	9	3	—	1	2	1	1	3	7	12	15	17	24	20	20	29	—	164	
Brain and other nervous system	191,192	16	13	10	5	6	8	7	7	8	13	20	18	30	19	14	11	—	205	14
Thyroid gland	193	1	—	2	4	16	17	14	13	13	11	18	15	9	7	9	14	1	164	
Lymphosarcoma and reticulosarcoma	200	2	1	1	2	4	9	5	5	12	15	22	27	32	37	31	57	1	263	12
Hodgkin's disease	201	—	1	5	13	16	13	10	4	6	5	6	4	4	8	5	8	—	108	
Other lymphomas	202	—	2	1	3	2	3	2	5	6	6	11	8	11	12	11	23	1	107	
Multiple myeloma	203	—	—	—	1	—	1	2	2	3	7	11	13	15	24	20	43	—	142	
Leukemia	204-207	23	12	8	10	9	8	8	7	14	12	19	23	22	32	35	79	1	322	10
Other and non-specific	Residual	13	2	2	7	12	13	15	23	38	52	79	88	101	126	124	312	14	1021	
TOTAL	140-207	75	40	43	87	213	477	519	588	805	1114	1363	1386	1483	1433	1354	2702	98	13780	

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[1] ICD8: International Classification of Diseases, Eighth Revision, World Health Organization, Geneva, 1967.
[2] Rank order for sites with more than 200 cases.

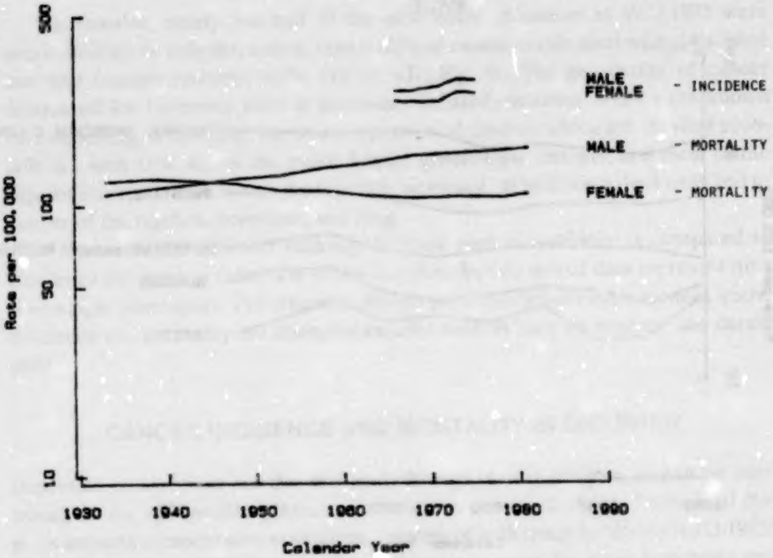

Fig. 3 Age-adjusted provisional incidence rates (1966-1975) and age-adjusted mortality rates (1931-1981) for all cancer sites, by sex, Ontario. (Age adjustment is to the world population.)

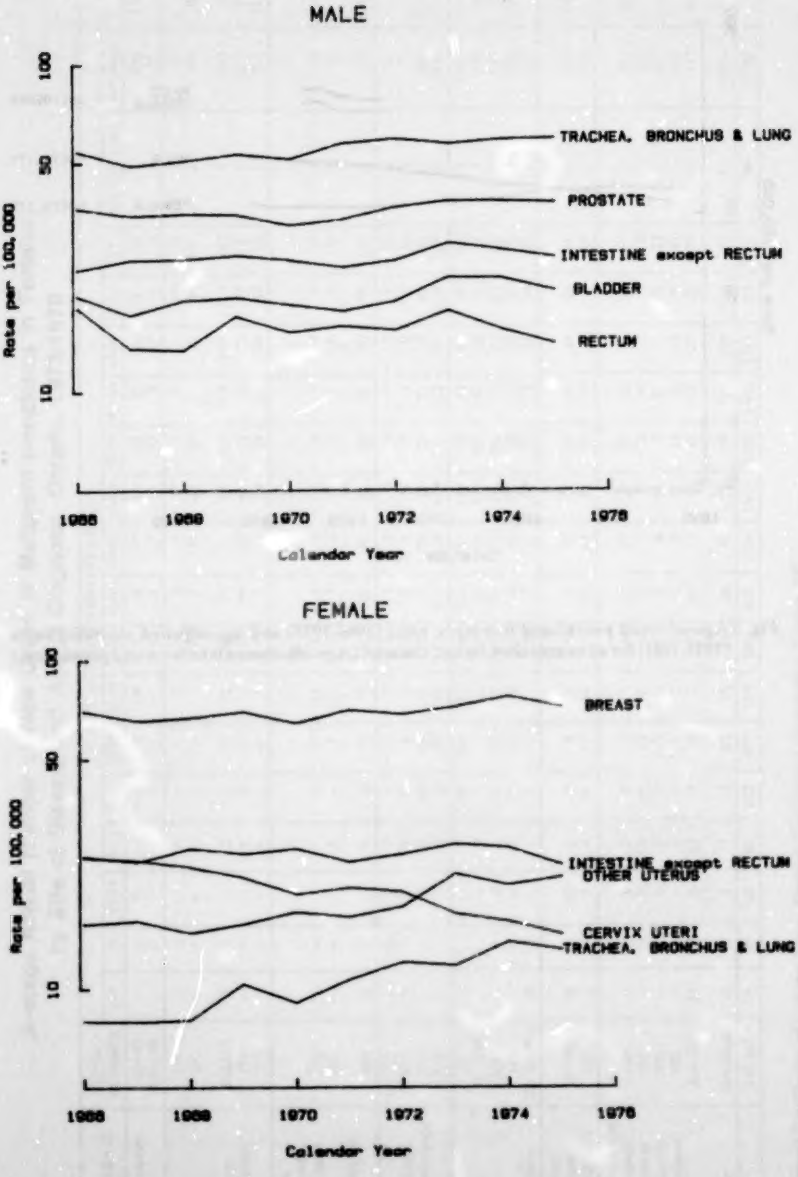

Fig. 4 Age-adjusted provisional incidence rates for selected cancer sites, by sex, Ontario, 1966-1975. (Age adjustment is to the world population.)

In females, nearly one-half of the new cases of cancer in 1973-1975 were accounted for by only three sites: breast (25% of cases), cervix uteri with (14%), and intestine (except rectum) (10%) (Table VII, Fig. 4). The proportion of cancer accounted for by cervix uteri is somewhat inflated, however, due to the known over-reporting of that site; the true proportion of cancers which are cervical probably is about 11%. All of the major female gynecologic cancers, and most of the digestive cancers, rank within the top 10 in incidence, in addition to leukemia and to cancer of the trachea, bronchus, and lung.

Of course, the different rankings of some sites in mortality as compared to incidence are partly a reflection of the fact that the two sets of data represent time points eight years apart. The effects of this are particularly noticeable for sites whose incidence and mortality are changing rapidly, such as lung (in women) and cervix uteri.

CANCER INCIDENCE AND MORTALITY IN CHILDREN

Important cancer sites are not the same throughout the lifespan, as can be seen readily in the age-specific frequency tabulations presented above. Table VIII displays important cancer sites in children, in terms of both crude incidence (1973-1975) and crude mortality (1982) rates. The leukemias account for more new cases and more deaths in children than any other cancer. Second-ranked in incidence and in mortality is cancer of the brain and other nervous system. Other rankings are dissimilar for incidence and mortality, although cancer of the bone (primarily osteosarcoma) ranks within the top five childhood cancers in both incidence and mortality in children. Some of these differences may be related to recent treatment improvements which would be reflected in current mortality rates.

POPULATIONS

Displayed in Table IX are three sets of population data: the 1974 and the 1982 estimated Ontario populations, and the world population. The 1974 Ontario data are given for the use of those who would compute age-specific rates based on the incidence frequencies shown in Tables VI and VII. The 1982 Ontario data are given for use with the mortality frequences in Tables I to IV. The world population is an artificial population which is used to age-adjust cancer rates. It can be used with both the incidence and mortality data and it allows comparison of Ontario rates with those from other areas, where the world population has been used as the standard for age-adjustment.

TABLE VIII

Malignant Neoplasms in Children Aged 0-14 Crude Rates of New Cases and Death Selected Sites, Ontario, 1974 and 1982

SITE OF DISEASE	ICD9[1] NUMBER	NEW CASE RATE PER 1,000,000 1974	DEATH RATE PER 1,000,000 1982
Lip and oral cavity	140-145	1.4	–[2]
Intestine, except rectum	152,153	2.3	–
Trachea, bronchus and lung	162	2.3	–
Bone	170	7.9	2.7
Connective tissue	171	5.6	1.6
Malignant melanoma	172	2.3	–
Kidney and ureter	189.0-189.2	9.8	–
Brain and other nervous system	191,192	37.4	12.3
Lymphosarcoma and reticulosarcoma	200	7.5	–
Hodgkin's disease	201	7.0	–
Other lymphomas	202	4.2	3.7
Leukemia	204-208	52.8	20.3

[1] ICD9 and ICD8 are directly comparable for all sites listed here except leukemia which is coded as sites 204-207 in ICD8.

[2] Indicates that fewer than two deaths occurred at that site in children in 1982, and therefore the rate is not calculated.

TABLE IX

World Standard Population and Estimated Population, 1974 and 1982, of Ontario (In Thousands)

AGE GROUP	WORLD STANDARD[1]	ONTARIO, 1974[2]		ONTARIO, 1982[2]	
	MALE OR FEMALE	MALE	FEMALE	MALE	FEMALE
0-4	12.0	323.5	307.1	305.8	291.6
5-9	10.0	354.9	338.1	312.6	296.7
10-14	9.0	418.8	398.3	343.7	325.8
15-19	9.0	392.5	380.0	402.3	382.8
20-24	8.0	350.2	354.4	400.0	401.8
25-29	8.0	335.0	335.4	365.6	382.9
30-34	6.0	274.8	268.5	352.4	362.3
35-39	6.0	240.2	234.4	312.9	312.0
40-44	6.0	244.4	233.7	254.0	252.3
45-49	6.0	236.4	235.6	235.4	231.4
50-54	5.0	218.9	227.7	236.8	233.8
55-59	4.0	168.6	176.2	218.2	233.5
60-64	4.0	150.3	159.5	177.9	198.3
65-69	3.0	112.9	132.4	142.6	167.2
70-74	2.0	82.3	104.9	104.7	134.5
75+	2.0	98.3	165.9	123.8	219.8
TOTAL	100.0	4002.0	4052.1	4288.7	4426.7

[1] Waterhouse, John et al (eds). Cancer Incidence in Five Continents, Vol IV. World Health Organization, Geneva, 1982, p.673.

[2] Source: Statistics Canada.

CANCER TREATMENT

Hospital Caseload

During the Ontario Ministry of Health's fiscal year 1981-1982, there were 66,130 separations (discharges and deaths) from active and rehabilitation hospitals in Ontario in which the primary diagnosis was cancer. These accounted for 5.2% of all hospital separations and 1,011,066 days of hospital care. The average length of stay for cancer patients declined from 19.8 days in 1970 to 15.8 days in 1981-82*.

New Cancer Cases Registered at the Foundation Treatment Centres

In the last decade, the number of new cases registered for the first time at the treatment centres has increased by 41% from 12,509 cases to 17,702 (Table X). To make this comparison over time, it has been necessary to take into account the introduction of the Ninth Revision of the International Classification of Diseases in 1979, in which the categories — in situ carcinoma and neoplasms of uncertain behavior — were separated from other malignant neoplasms. In addition, in 1981, the Foundation returned to the international practice of counting patients with skin cancer as having only two lesions — basal cell or squamous cell cancer — and not as having multiple cancers of the same histology in different body sites. The distribution by treatment centre of the numbers of the situ lesions, neoplasms of uncertain behavior and multiple skin cancers is shown at the foot of Table XI.

It should be noted that a new case registered for the first time at the Foundation treatment centres refers to a case of cancer seen for the first time during a year at any one of the Foundation centres. If a case is seen at two treatment centres in the same year, it is only considered in this table as being seen by the first centre. It should also be realized that a case may be new to the Foundation but may have been diagnosed some years before admission and be referred with metastatic disease; approximately 10% of newly registered cases fall into this category.

In Table XI, for 1982, the major sites of newly registered cancers were lung, bronchus and trachea (15.7%) and breast (15.7%) followed by skin, other than malignant melanoma (11.5%). Of the 16,205 cancers seen for the first time at one of the treatment centres, 14.1% were seen in Hamilton, 5.7% in Kingston, 13.2% in London, 13.1% in Ottawa, 2.6% in Thunder Bay, 4.7% at Toronto-Bayview, 5.0% in Windsor and 41.6% at the Princess Margaret Hospital in Toronto.

The location of the regional treatment centres and the associated peripheral clinics determines the referral pattern to each centre (Table X). Thus, of the 209 residents of Kent County who were seen at a treatment centre, 21 were seen at the Windsor Clinic, two at the Princess Margaret Hospital, four at the Hamilton Clinic and the remaining 182 at the London Clinic. In addition to Ontario residents, 414 residents of Quebec were referred to the Foundation centres — the majority of these being seen at the Ottawa Clinic. An additional 104 residents of other provinces were

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*Hospital Statistics 1981/82 published by the Ontario Ministry of Health.

TABLE X*

New Cancer Cases Registered by Treatment Centre, 1973-1982[1,2]

CENTRE	YEAR OF REGISTRATION									
	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982*
Hamilton	1,890	1,890	2,091	2,254	2,353	2,493	2,594	2,507	2,537	2,688
Kingston	932	887	921	816	988	1,040	999	984	997	1,073
London	2,111	2,254	2,359	2,460	2,344	2,488	2,537	2,583	2,529	2,563
Ottawa	1,423	1,502	1,525	1,631	1,759	1,902	1,997	2,078	2,190	2,248
Thunder Bay	300	313	313	399	365	412	369	401	462	444
Toronto-Bayview	—	—	—	—	—	—	—	441	504	816
Toronto, PMH	5,083	5,569	6,027	6,158	6,462	6,960	6,911	7,057	7,320	7,012
Windsor	770	857	889	880	843	854	898	813	907	858
TOTAL	12,509	13,272	14,125	14,598	15,114	16,149	16,305	16,864	17,446	17,702

*Provisional (transition period — see text).

[1] Excludes carcinoma of cervix in situ.

[2] Any case registered at more than one treatment centre in a given year is allocated to the centre where it was first registered.

TABLE XI*

New Cancer Cases Registered by Site of Disease and Treatment Centre, 1982

SITE OF DISEASE	ICD9[1] NUMBER	TREATMENT CENTRE								TOTAL	
		Hamilton	Kingston	London	Ottawa	Thunder Bay	Toronto		Windsor	Number	Per Cent
							Bayview	PMH			
Lip	140	11	15	16	10	4	1	38	7	104	0.6
Tongue	141	16	5	14	21	1	17	79	3	156	1.0
Rest of Mouth	142-145	33	12	42	36	4	27	140	12	306	1.9
Pharynx and tonsil	146-149	29	13	38	28	4	12	137	10	271	1.7
Esophagus	150	21	13	24	23	3	9	84	8	185	1.1
Stomach	151	31	5	21	30	8	17	80	16	208	1.3
Intestine, except rectum	152,153	81	16	77	116	29	38	193	46	596	3.7
Rectum and anal canal	154	93	33	58	71	16	15	272	30	588	3.6
Other digestive system	155-159	35	19	38	45	16	23	88	30	294	1.8
Nose, middle ear and accessory sinuses	160	9	7	7	7	—	7	24	1	62	0.4
Larynx	161	45	22	35	41	7	18	183	11	362	2.2
Lung, bronchus and trachea	162	312	156	318	340	68	118	1092	145	2549	15.7
Other respiratory	163-165	12	2	4	3	1	3	18	—	43	0.3
Bone	170	8	2	4	4	1	4	17	3	43	0.3
Malignant melanoma	172	51	16	32	50	4	86	141	9	389	2.4
Other cancer of skin	173	329	184	351	153	46	67	620	111	1861	11.5
Breast	174,175	368	137	319	412	62	76	1050	126	2550	15.7
Cervix uteri	180	49	17	52	60	15	5	203	10	411	2.5
Other uterus	179,181,182	96	23	115	101	10	3	224	25	597	3.7
Ovary, tubes and ligament	183	55	22	52	37	12	8	197	16	399	2.5
Other female genital organs	184	11	9	7	15	2	—	27	1	72	0.4
Prostate	185	109	43	82	78	24	24	283	19	662	4.1
Testis	186	17	2	13	18	2	1	87	8	148	0.9
Other male genital organs	187	2	—	3	3	—	2	7	—	17	0.1
Bladder	188	70	30	57	47	11	16	211	30	472	2.9
Kidney, other urinary	189	32	13	33	40	11	14	88	15	246	1.5
Brain and nervous system	191,192	37	15	64	46	10	29	160	14	375	2.3
Thyroid gland	193	10	1	10	5	2	3	44	2	77	0.5
Lymphosarcoma and reticulum-cell sarcoma	200	45	17	52	49	10	25	177	10	385	2.4
Hodgkin's disease	201	27	14	31	35	5	17	118	11	258	1.6
Other lymphomas	202	63	11	25	48	6	18	94	9	274	1.7
Leukemia	204-208	55	8	43	32	15	6	140	30	329	2.0
Other sites	Residual	117	39	102	113	19	57	428	41	916	5.7
TOTAL		2279	921	2141	2117	428	766	6744	809	16205	100.0
Cervix uteri (in situ)	233.1	2	1	2	4	2	1	6	2	20	—
Other sites (in situ)	230-234	34	13	42	30	4	26	60	9	218	—
Neoplasms of uncertain behaviour	235-238	23	1	11	14	5	8	59	8	129	—
Multiple skins (see text)	173	352	138	369	87	7	16	149	32	1150	—

*Provisional (transition period — see text)

[1] ICD9: International Classification of Diseases (Ninth Revision)

TABLE XII*

New Cancer Cases Registered by Place of Residence and Treatment Centre, 1982

COUNTY OR DISTRICT	TREATMENT CENTRE								TOTAL
	Hamilton	Kingston	London	Ottawa	Thunder Bay	Toronto		Windsor	
						Bayview	PMH		
Algoma	–	–	12	–	3	3	139	–	157
Brant	195	–	6	–	–	–	10	–	211
Bruce	1	–	78	–	–	2	52	–	133
Carleton	2	3	1	1045	–	1	3	–	1055
Cochrane	2	1	–	16	2	6	144	–	171
Dufferin	2	–	–	–	–	7	51	–	60
Dundas	–	3	–	23	–	–	1	–	27
Durham²	1	1	–	1	–	26	317	–	346
Elgin	1	–	134	–	–	–	2	–	137
Essex	1	–	37	–	–	1	5	780	824
Frontenac	–	264	–	3	–	–	5	–	272
Glengarry	–	4	–	42	–	–	1	–	47
Grenville	–	38	–	26	–	–	3	–	67
Grey	–	–	40	–	–	2	101	–	143
Haldimand-Norfolk¹	116	–	51	–	–	–	4	–	171
Haliburton	–	1	1	–	–	1	25	–	28
Halton	251	2	–	2	–	3	133	–	391
Hastings	1	195	2	1	–	4	52	–	255
Huron	–	–	98	–	–	–	4	–	102
Kenora	–	–	–	1	33	–	1	–	35
Kent	4	–	182	–	–	–	2	21	209
Lambton	3	–	262	–	–	–	6	–	271
Lanark	–	30	–	81	–	–	2	–	113
Leeds	1	133	–	7	–	–	3	–	144
Lennox and Addington	–	82	–	2	–	–	2	–	86
Manitoulin	1	–	–	–	–	–	17	–	18
Middlesex	4	–	625	2	1	–	6	–	638
Muskoka	1	–	–	1	–	4	89	1	96
Niagara¹	498	1	3	1	–	14	166	–	683
Nipissing	–	1	–	5	–	2	173	–	181
Northumberland²	–	20	–	–	–	4	94	–	118
Oxford	2	–	184	–	–	–	3	–	189
Parry Sound	1	–	–	–	–	7	57	–	65
Peel	14	–	5	–	–	19	527	–	565
Perth	–	3	151	–	–	–	4	–	158

(Continued on opposite page)

TABLE XII* (Continued)

New Cancer Cases Registered by Place of Residence and Treatment Centre, 1982

COUNTY OR DISTRICT	TREATMENT CENTRE								TOTAL
	Hamilton	Kingston	London	Ottawa	Thunder Bay	Toronto		Windsor	
						Bayview	PMH		
Peterborough[2]	—	4	—	—	—	16	184	1	205
Prescott	—	—	—	49	—	—	—	—	49
Prince Edward	—	63	—	—	—	—	7	—	70
Rainy River	—	—	1	—	48	—	2	—	51
Renfrew	1	3	—	185	—	—	4	—	193
Russell	7	—	—	44	—	—	—	—	51
Simcoe[2]	7	1	3	—	—	32	387	—	430
Stormont	—	18	—	109	—	—	—	—	127
Sudbury	1	1	6	3	1	2	226	1	241
Thunder Bay	1	—	2	1	330	2	21	—	357
Timiskaming	3	—	—	5	—	7	57	—	72
Victoria[2]	—	—	—	—	—	18	92	—	110
Waterloo	48	—	203	—	—	2	66	—	319
Wellington	137	—	24	—	—	1	42	—	204
Wentworth	944	—	1	1	—	1	12	—	959
York	5	5	8	8	—	549	3258	—	3833
Quebec	6	4	3	385	—	3	12	1	414
Other Provinces	8	3	8	39	8	12	80	2	160
U.S.A.	5	35	4	16	2	6	22	1	91
Other	4	2	6	13	—	9	68	1	103
TOTAL	2279	921	2141	2117	428	766	6744	809	16205

*Provisional (transition period — see text).

[1] In 1971 the counties of Welland and Lincoln became the Regional Municipality of Niagara.

[2] In 1974 the counties of Durham and Ontario became the Durham Regional Municipality. Also the counties of Simcoe, Peterborough, Northumberland and Victoria have been expanded by parts of Durham and Ontario.

[3] In 1974 the counties of Haldimand and Norfolk became the Regional Municipality of Haldimand-Norfolk.

seen at the Foundation centres mainly at the Princess Margaret Hospital. Of the 91 residents of the United States and other countries, 35 were referred to the Kingston Clinic and 22 to the Princess Margaret Hospital.

Seminars in Cancer Epidemiology

The Foundation held three seminars in the last academic year. In November 1982, Dr. H. Shannon and Mr. J. Julian presented "Mortality Studies of Nickel Workers"; in January 1983, Dr. L. Jupper presented "How Useful are Modern Statistical Methods in Cancer Epidemiology"; in May 1983, the subject was "The Problem in the Measurement of Environmental Health Effects", Dr. I. Broder and Professor P. Corey presented a discussion on urea formaldehyde foam insulation, and Dr. R. Steel and Dr. R. Lees presented the problem of studying chemical pollutants in a water supply.

ACKNOWLEDGEMENTS

The continuing co-operation of government is gratefully acknowledged; the Ontario Ministry of Health has provided source records and advice; the Office of the Registrar General of the Ministry of Consumer and Commercial Relations has provided computerized data on deaths due to all causes in Ontario residents and, in addition, has provided facilities so that a large number of their records can be searched for the purpose of treatment evaluation and research. We have appreciated greatly the assistance of the staff of the Hospital Medical Records Institute (HMRI) and all the individual hospitals in Ontario, which they have not only assisted in the interpretation of data from this source but also have provided additional information.

Our personal thanks are due to the Directors of the regional treatment centres and the Princess Margaret Hospital and their Heads of Medical Records for their support during the year and to the members of the Foundation's Standing Committee on Records and Statistics and the sub-committees.

We acknowledge with gratitude the assistance of all the staff of Information Systems in the processing of the Foundation's large data base, particularly in the generation of incidence data for 1964 to 1975.

Our special thanks are also extended to Mrs. Mary Nemes, Head of Medical Records in the Division, and to the staff of the Division for their help in the generation of the incidence data and their continual efforts to upgrade the cancer registry. We are also grateful to Mrs. Nemes for her help in the preparation of this report and to the staff of the Research Unit, located at the University of Toronto, for the combination of statistical and clerical skills required for the completion of this report.

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APPENDIX A

BEQUESTS AND OTHER DONATIONS

The Foundation was the grateful recipient of legacies, bequests and other donations totalling $2,052,971 in 1982, which are of inestimable value to the Foundation's program.

Legacies of $1,000 or over were received from the following estates:

The late Thomas Richard J. Allin, Toronto	$ 1,517	(part)
— Gladys Earline Armstrong, Ottawa	18,829	
— Mattie Helen Ball, St. Thomas for use at London Clinic	12,500	(part)
— Ethel Maud Bauckham, Toronto	1,000	
— Paul Bespalko, Toronto	10,000	
— Pearl Bingham, Cambridge	19,800	(part)
— Dr. Russell G. Birrell, Toronto for research	70,000	(part)
— Mary Hilda Blackwell, Hamilton	7,496	(part)
— Ina Sara Bolduc, Toronto	5,000	
— Olive Boudreau, North Bay for research	1,000	
— John Sidney Burton, London for research at London Clinic	7,232	(part)
— Frank Carruthers, Guelph	16,785	(part)
— William Daniel Cavanaugh, Parkhill for use at London Clinic	56,439	
— Frances E. W. Coleman, Ottawa	33,646	(part)
— Margaret Kathleen Coleman, Toronto	1,000	
— Ivan Coulter, Leamington	17,890	
— John MacKenzie Dow, Township of Fullerton, County of Perth, for research	50,000	(part)
— Eldred Durham, Toronto (Ann and Eldred Durham Trust Fund) for research	7,909	
— Doris Margaret Esdale, Ottawa	4,629	(part)
— John Jacob Freedman, Toronto	60,000	(part)
— Nell C. Gerrie, Toronto	2,000	

– Irene M. Greenway, St. Thomas for leukemia program at London Clinic	1,000	
– Ruth Goddard Greenslade, London for use at London Clinic	36,650	
– Lottie Elizabeth Hamilton, Wyoming for research	3,018	
– Irene Victoria Howard, Richmond Hill	3,000	
– Martin Jalkanin, Nipigon for use at Thunder Bay Clinic	3,000	
– Rhoda Owen Jenkin, Kingston for use at Kingston Clinic	1,000	
– May Johnston, London for research at London Clinic	1,000	(part)
– Ruby Elizabeth Julian, Brampton	13,192	(part)
– Annie Augusta Kates, Toronto	10,000	(part)
– Louis Phillippe Lachance, Weston for research	9,396	
– Florence Jane Lock, Sault Ste. Marie	8,698	
– Birdie Muriel Lounsbury, Brantford	34,500	(part)
– Mary I. Malloney, Toronto	1,800	(part)
– Lena Marie Marsh, Newmarket	240,000	(part)
– Isabel Elizabeth Matheson, Goderich	32,500	(part)
– Earl McDermid, Toronto	1,000	
– Clara Jane McNaughton, Watford for research at London Clinic	10,389	(part)
– Ellen May McVicar, London for research at London Clinic	26,000	(part)
– John Stanley Meredith, London (Jessie Meredith Memorial Trust Fund) for cancer research	481,403	(part)
– Clara Freda Nodwell, Toronto	73,000	(part)
– William Edwin Nodwell, Toronto	70,059	(part)
– John Samuel Perks, St. Catharines	2,000	
– Estella Margaret Reekie, Thornbury	26,410	
– Bertha M. Richter, London (Richter Endowment Fund Trust) in memory of Martha Ann Richter and George Richter, for use at London Clinic	152,000	(part)
– Donald Cameron Routledge, London for research at London Clinic	2,875	(part)
– Marjorie T. Roy, Ottawa for research	20,000	

— Clara B. Sanderson, Brantford (John A. Sanderson and Family Trust)	8,225	(part)
— Olga Schonfeld, Windsor	7,000	(part)
— Henrietta May Shoalts, Welland	8,469	
— Dorothy Adeline Standing, Toronto for research	5,724	(part)
— Louis Szel, Toronto for research	19,608	(part)
— Elizabeth Taylor, Orillia	7,999	(part)
— Ester Pearl Van Horne, Sarnia	2,500	
— Edward Clive Watson, Ottawa for use at Ottawa Clinic Civic Hospital Division	25,000	(part)
— Lulu May West, Toronto	18,226	
— John White, Hamilton	2,653	(part)
— John Whittle, London for use at London Clinic	25,000	(part)
— Madeleine Wilson, St. Mary's for research at London Clinic	1,887	(part)

Donations of $1,000 or more were received from the following:

— Canadian Breakers C.B. Club, Amherstburg	$ 1,050
— C.E. Corcoran, Toronto	1,000
— Daughters of Penelope, Mykene Chapter No. 339 Windsor, for use at Windsor Clinic	1,417
— James Dennett Ltd., Corunna for research	1,000
— Hamilton Radiotherapy Associates Group for Dr. Robert G. MacLaren Memorial Fund	2,700
— Kiwanis Club of South Ottawa for use at Ottawa Clinic	3,000
— Norah J. Logan, Sarnia for use at Ottawa Clinic	2,870
— Mary MacLennan, Windsor for research	1,000
— Paul Mellon Enterprises Limited, Sarnia for use at London Clinic	1,500
— Stella Mendleson and Family, Kanata for use at Ottawa Clinic	1,000
— Mrs. John P. Morawetz, Don Mills	1,378
— Jack New, Thunder Bay	1,000

– Order of the Eastern Star Capital City Chapter No. 172, Ottawa for use at Ottawa Clinic	1,100
– Ottawa Medical Associates Group	1,000
– Lillian Roughton, Kingston for research	1,000
– St. Clair Ladies' Club, Windsor for use at Windsor Clinic	2,172
– W. P. Scott Charitable Foundation, Toronto for research	1,000
– The Toronto Star, Toronto	1,000
– H. G. Vail Family Holding Ltd., Ottawa (Harold Vail Visiting Professorship Fund) for use at Ottawa Clinic	15,000
– M.G.M. Wilson, London for the Harold E. Johns Summer Studentships in Medical Physics Program	1,466
– George Winter, Mount Brydges for research	2,000
– H. Wrigglesworth, Don Mills (Dorothy Wrigglesworth Cancer Research Fund)	1,000

The Foundation is grateful to these donors and to the many others not listed above and reveres the memory of those who extended their lifetime efforts to fight cancer when making their wills. These welcome additions to our research and other funds ensure that the Foundation's extensive research program can proceed at a time of financial constraints and inflated costs.

APPENDIX B

LIST OF ARTICLES PUBLISHED 1982

RESEARCH ASSOCIATES AND GRANTEES, AND MEMBERS OF THE STAFFS OF THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION AND THE REGIONAL TREATMENT CENTRES

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University of Toronto

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NUMBER

2

THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION

1943 — 1983
FORTY YEARS OF SERVICE TO CANCER PATIENTS

7 Overlea Boulevard
Toronto, Ontario M4H 1A8
(416) 423-4240

M.A. MEIGHEN, Q.C. Chairman
Dr. J.W. MEAKIN Executive Director
R.T. GRAY Secretary-Treasurer

April 15, 1984

The Honourable Keith C. Norton
Minister of Health for Ontario
Queen's Park
Toronto, Ontario
M7A 2C4

Dear Mr. Minister:

On behalf of the Members of The Ontario Cancer Treatment and Research Foundation, and in accordance with paragraph 13(1) of The Cancer Act, I am pleased to submit the publication "Cancer in Ontario 1982" and the enclosed audited financial statements for the year ended March 31, 1983 as the Annual Report of the Foundation for the fiscal year ended March 31, 1983.

Upgrading and updating of the Cancer Registry is nearing completion. By December 1984, data will be available on the occurrence of each new case of cancer in Ontario from 1964 to 1982. The world's first "Therac 25" linear accelerator, designed and developed in Ontario as "state of the art" in radiotherapy technology, was installed in the Toronto-Bayview Clinic.

The Members of the Board are appreciative of the support of your Ministry, the efforts of the Foundation staff and all others who have, by their dedication and continuing efforts, contributed to a brighter future for Ontario's cancer patients.

Yours sincerely,

Michael A. Meighen

M.A. Meighen, Q.C.
Chairman

THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION

FINANCIAL STATEMENTS
FOR THE YEAR ENDED MARCH 31, 1983

Ontario

Office of the
Provincial
Auditor

Parliament Buildings
Queen's Park
Toronto, Ontario
M7A 1A2
416/965-1381

To The Ontario Cancer Treatment and Research Foundation and
to the Minister of Health.

I have examined the balance sheet of The Ontario Cancer Treatment and Research Foundation as at March 31, 1983 and the statements of capital and endowment fund revenue and expenditure, capital and endowment fund, research and other special purposes funds, clinic construction fund and changes in funds financial position for the year then ended. My examination was made in accordance with generally accepted auditing standards, and accordingly included such tests and other procedures as I considered necessary in the circumstances.

Bequests and donations to the Foundation, by their nature, are not susceptible to complete audit verification. Accordingly, my verification of receipts from these sources was limited to the amounts recorded by the Foundation in the accounting records.

In my opinion, except for the effect of any adjustments which might have been required had I been able to completely verify bequests and donations, these financial statements present fairly the financial position of the Foundation as at March 31, 1983 and the results of its operations for the year then ended in accordance with the basis of accounting described in note 1 to the financial statements applied, after giving retroactive effect to the change in the method of accounting for investment income as referred to in note 2, on a basis consistent with that of the preceding year.

A report on the audit has been made to the Foundation and to the Minister.

J.F. Otterman

Toronto, Ontario,
August 26, 1983.

J.F. Otterman, C.A.,
Assistant Provincial Auditor.

STATEMENT 1

THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION

Balance Sheet
as at March 31, 1983

ASSETS	1983 $	1982 $
CURRENT		
Cash	731,142	765,586
Investments (notes 1c and 3)	23,962,610	16,513,036
Accrued investment income (note 2)	311,011	346,879
Accounts receivable	245,430	200,236
Due from the Province of Ontario (note 5)	1,154,778	3,340,733
Prepaid expenses	61,543	108,904
	26,466,514	21,275,374
OTHER		
Advances to The Ontario Cancer Institute	175,000	175,000
Fixed assets (notes 1d and 4a)	11,335,074	8,919,607
Deposits on equipment (note 4b)	1,690,338	1,346,500
	13,200,412	10,441,107
	39,666,926	31,716,481

LIABILITIES AND FUND BALANCES	1983 $	1982 $
CURRENT		
Accounts payable	4,052,132	3,266,733
Deferred revenue (note 6)	600,000	-
	4,652,132	3,266,733
FUNDS (note 1a)		
Capital and endowment (statement 3)	26,079,131	20,719,599
Research and other special purposes (statement 4)	6,322,760	5,094,093
Clinic construction (statement 5)	2,612,903	2,636,056
	35,014,794	28,449,748
	39,666,926	31,716,481

See accompanying notes and schedule to financial statements.

On behalf of the Foundation:

Michael A. Naylor
Chairman

Secretary-Treasurer

STATEMENT 2

THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION

Capital and Endowment Fund
Statement of Revenue and Expenditure
for the year ended March 31, 1983

	1983 $	1982 $
REVENUE		
Province of Ontario		
Operation of treatment clinics (note 5)	19,180,667	14,306,213
Cancer control programs	8,866,500	6,575,425
Research	3,213,000	2,843,469
Treatment clinics	1,335,643	980,318
Donations and legacies (note 1b(i))	945,000	646,447
Investment income (note 2)	1,547,520	2,211,153
Total revenue	35,088,330	27,563,025
EXPENDITURE		
Treatment clinics, including certain cance. control expenditure (schedule)	23,495,238	18,637,685
Cancer control programs		
Grant to The Ontario Cancer Institute	1,642,441	1,178,569
Grants for miscellaneous cancer control programs	926,880	732,315
Operation of hostels by treatment clinics	1,531,747	1,380,397
Assistance to cancer patients	842,227	700,116
Sundry clinical expenses	249,875	139,259
General, administrative and statistical expenses	2,122,081	1,754,861
	7,315,251	5,885,517
Research		
Grant to The Ontario Cancer Institute	1,912,879	1,723,273
Other grants and expenses	1,580,205	1,687,595
	3,493,084	3,410,868
Total expenditure	34,303,573	27,934,070
Excess (deficiency) of revenue over expenditure (note 2)	784,757	(371,045)

See accompanying notes and schedule to financial statements.

STATEMENT 3

THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION

Statement of Capital and Endowment Fund for the year ended March 31, 1983

	1983 $	1982 $
Balance, beginning of year	20,719,599	15,785,485
Add: Grants from the Province of Ontario	4,416,394	4,299,433
Transfers from research and other special purposes funds (statement 4)		
For research from research fund	131,010	660,962
For equipment purchases from		
Other special purposes fund	27,371	322,287
Research fund	-	22,477
	27,371	344,764
Excess (deficiency) of revenue over expenditure (statement 2)	784,757	(371,045)
Balance, end of year	26,079,131	20,719,599
Represented by:		
Investment in fixed assets	11,335,074	8,919,607
Deposits on equipment	1,690,338	1,346,500
Reserve for equipment ordered and to be paid for from funds on hand	693,990	693,932
Endowment fund	12,359,729	9,759,560
	26,079,131	20,719,599

See accompanying notes and schedule to financial statements.

STATEMENT 4

THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION

Statement of Research and Other Special Purposes Funds for the year ended March 31, 1983

		1983 $	1982 $
RESEARCH FUND			
Balance, beginning of year		2,527,965	1,191,610
Add:	Donations (note 1b(i))	803,692	373,089
	Investment income	317,827	379,252
	Transfer from clinic construction fund (statement 5)	-	800,000
	Grant from the Province of Ontario	-	500,000
		1,121,519	2,052,341
Less:	Transfer to capital and endowment fund (statement 3)		
	For research expenses	131,010	660,962
	For equipment purchases	-	22,477
	Miscellaneous research expenses	76,557	32,547
		207,567	715,986
Balance, end of year		3,441,917	2,527,965

THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION

Statement of Research and Other Special Purposes Funds for the year ended March 31, 1983

		1983 $	1982 $
OTHER SPECIAL PURPOSES FUND			
Balance, beginning of year		2,566,128	2,082,352
Add:	Donations (note 1b(i))	423,425	688,140
	Investment income	119,787	117,080
	Grant from the Provincial Lottery	1,223,982	-
	Grant from the World Health Organization	49,726	-
	Grant from the Ontario Division, Canadian Cancer Society	-	400,000
		1,816,920	1,205,220
Less:	Transfer to capital and endowment fund for equipment purchases (statement 3)	27,371	322,287
	Grant to The Ontario Cancer Institute for nuclear magnetic resonance imaging equipment	1,223,982	-
	Sudbury tumour registry	72,262	37,635
	Grant to the Sunnybrook Hospital for equipment purchases	26,962	31,200
	Computer service expenses	-	152,300
	Miscellaneous expenses	151,628	178,022
		1,502,205	721,444
Balance, end of year		2,880,843	2,566,128
		6,322,760	5,894,093

See accompanying notes and schedule to financial statements.

STATEMENT 5

THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION

Statement of Clinic Construction Fund for the year ended March 31, 1983

	1983 $	1982 $
Balance, beginning of year	2,636,056	4,471,719
Add: Investment income	273,009	475,145
Less: Design, planning and construction costs at various clinics	296,162	1,510,808
Transfer to research and other special purposes funds for research (statement 4)	-	900,000
	296,162	2,310,808
Balance, end of year	2,612,903	2,636,056

See accompanying notes and schedule to financial statements.

STATEMENT 6

THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION

Statement of Changes in Funds Financial Position for the year ended March 31, 1983

	1983 $	1982 $
Source of funds		
From operations		
Excess (deficiency) of revenue over expenditure	784,757	(371,045)
Depreciation not requiring an outlay of funds in the current year	1,343,137	912,904
Fund receipts		
Capital and endowment	4,574,775	5,305,159
Research and other special purposes	2,938,439	3,257,561
Clinic construction	273,009	475,145
	9,914,117	9,579,724
Use of funds		
Capital and endowment		
Purchase of fixed assets, net (note 7)	3,758,604	4,271,962
Deposits on equipment	343,838	879,479
Research and other special purposes	1,709,772	1,437,430
Clinic construction	296,162	2,310,808
	6,108,376	8,899,679
Increase in working capital	3,805,741	680,045
Working capital, beginning of year	18,008,641	17,328,596
Working capital, end of year	21,814,382	18,008,641

See accompanying notes and schedule to financial statements.

THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION

Notes to Financial Statements
as at March 31, 1983

1. SIGNIFICANT ACCOUNTING POLICIES

The financial statements of The Ontario Cancer Treatment and Research Foundation (the Foundation) present the financial position and results of its operations within the framework of the accounting policies summarized below:

(a) Fund Accounting

The accounts of the Foundation are maintained in accordance with the principles of fund accounting. Accordingly, resources for various purposes are classified for accounting and reporting purposes into three funds. Transfers between these funds are made as required.

(i) Capital and Endowment Fund

The capital and endowment fund includes the ordinary day-to-day operating transactions of the Foundation. Revenue of this fund consists of grants from the Province of Ontario, income from investments and its clinics together with donations and legacies which have no restriction on their use. In addition to normal operating expenditures, grants for special purposes may be made from this fund subject to approval by the members of the Foundation. The balance of the capital and endowment fund is the equity of the Foundation, and comprises its investment in fixed assets of $13,719,402 with the balance of $12,359,729 available for operating expenditures in excess of Provincial funding.

(ii) Research and Other Special Purposes Funds

Donations or grants which have restrictions placed on their use are credited directly to these funds. Where it is appropriate for the fund to earn income, investment income is allocated to it. In many cases only the investment income earned by these funds is available for use of the Foundation. Disbursements from these funds are made in accordance with the terms associated with donations or grants.

1. SIGNIFICANT ACCOUNTING POLICIES (cont'd)

(a) Fund Accounting (cont'd)

(iii) Clinic Construction Fund

The clinic construction fund represents funds held for major construction projects. Income is allocated to it from the investment income earned by the Foundation. Disbursements are made as approved by the members of the Foundation. Costs for construction of cancer clinics are charged directly to this fund and therefore do not form part of the fixed asset costs.

(b) Revenue and Expenditure

(i) Revenue of capital and endowment, research and other special purposes, and clinic construction funds is recorded on the accrual basis except that bequests and donations, due to their nature, are included in revenue as received.

(ii) Expenditures of capital and endowment, research and other special purposes, and clinic construction funds are recorded on the accrual basis when goods or services are acquired in the current fiscal year.

(c) Investments

Investments are reflected at cost with the exception of those received as part of legacies which are shown at market value on the date of receipt.

(d) Fixed Assets

Depreciation of fixed assets, with the exception of radium which does not depreciate, is provided for on a straight line basis using the following rates.

Office furniture and general equipment	10%
Computer equipment	20%
Therapeutic and other technical equipment in service	10%
Radioactive cobalt	20%

1. SIGNIFICANT ACCOUNTING POLICIES (cont'd)

(d) Fixed assets (cont'd)

Land and buildings donated to the Foundation by the Ontario Division, Canadian Cancer Society are recorded at nominal value.

2. CHANGE IN ACCOUNTING POLICY

In 1983, the Foundation changed its method of recording investment income from the cash basis to the accrual basis. This change has been given retroactive effect and the 1982 comparative figures have been restated, resulting in an increase of $36,355 in investment income for that year.

3. INVESTMENTS

	1983 $	1982 $
Short term investments, at cost (which is equivalent to market)	7,658,146	5,022,913
NHA mortgages (market value $290,000; 1982 - $398,700)	272,425	416,878
Bonds and debentures (market value $12,407,918; 1982 - $6,350,887)	12,305,321	7,084,459
Stocks (market value $4,041,670; 1982 - $3,082,802)	3,726,718	3,988,786
	23,962,610	16,513,036

4. FIXED ASSETS

(a)

	1983		1982	
	Cost $	Accumulated Depreciation $	Cost $	Accumulated Depreciation $
Office furniture, general and computer equipment	4,224,437	1,241,936	3,020,763	889,645
Therapeutic and other technical equipment in service	12,717,449	4,606,205	10,487,122	3,933,677
Radioactive cobalt	390,900	194,366	364,213	178,664
Radium	44,787	-	49,487	-
	17,377,573	6,042,507	13,921,585	5,001,986
	6,042,507		5,001,986	
	11,335,066		8,919,599	
Land and buildings, at nominal value	8		8	
	11,335,074		8,919,607	

(b) As at March 31, 1983 the Foundation has outstanding contractual commitments to acquire equipment in the amount of $2,939,921. The Foundation has recovered $2,384,328 from the Province of Ontario, and paid $1,690,338 as a down payment.

5. GRANT FOR THE OPERATION OF TREATMENT CLINICS

The grant of $21,371,311 from the Province of Ontario for the operation of treatment clinics in 1982-83 exceeded actual operating costs by $2,190,644. This grant has been shown in the capital and endowment fund, statement of revenue and expenditure at actual operating costs ($19,180,667). The excess of $2,190,644 less an amount of $600,000, which the Ministry of Health permitted the Foundation to retain for special purposes, has been offset against an amount of $2,745,668 due from the Province of Ontario for equipment purchases.

6. DEFERRED REVENUE

The Ministry of Health has allowed the Foundation to retain $600,000 of the excess funding for the operation of its treatment clinics during the 1982-83 year. This amount is to be used in the development of services in Sudbury, the carrying out of a Provincial Role Study on Cancer Services and the upgrading of the Ontario Cancer Registry. It is anticipated that these funds will be used for these purposes in 1983-84.

7. OPERATION AND ADMINISTRATION

As of March 31, 1983, the Foundation transferred the equipment of the Ottawa Clinic Nuclear Medicine Department to the Ottawa Civic Hospital at no cost. The transfer resulted in a loss on disposal of fixed assets of $231,237.

8. PENSION PLAN

The Foundation has a voluntary pension plan for its employees. Based on the most recent actuarial valuation of the plan as at July 1, 1982, the plan has a surplus of $697,831.

9. COMPARATIVE FIGURES

Comparative figures have been reclassified where necessary to conform with 1983 presentation.

SCHEDULE

THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION

Expenditures of Treatment Clinics for the year ended March 31, 1983

Clinic	Salaries & Benefits	Clinical Supplies	Operation & Administration (note 7)
	$	$	$
Hamilton	2,840,774	436,532	480,217
Kingston	1,763,408	72,105	379,023
London	2,843,470	393,384	487,878
Ottawa	4,294,112	978,496	1,270,565
Thunder Bay	860,840	123,854	198,458
Toronto Bayview	1,890,614	239,876	899,896
Windsor	1,338,014	329,451	239,487
	15,831,232	2,573,698	3,955,524

See accompanying notes to financial statements.

SCHEDULE (Cont'd)

	1983	1982
Depreciation	Total	Total
$	$	$
121,908	3,879,431	3,180,582
134,928	2,349,464	2,202,549
158,776	3,883,508	3,100,096
372,543	6,915,716	5,689,874
75,783	1,258,935	1,060,258
197,801	3,228,187	1,610,368
73,045	1,979,997	1,793,958
1,134,784	23,495,238	18,637,685